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NEUROPATHOLOGICAL PAPERS

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XIII. Dementia Praecox, Paranoid, Associated with Bronchiectatic Lung Disease and Terminated by Brain Abscesses (Micrococcus Catarrhalis.)
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(From Boston Medical and Surgical Journal, clix, 27, December, 1908.)

XIV. List of Thirty-seven Neuropathological Papers, Harvard University Medical School, 1904–1908.

NOTE.

These papers represent work done during 1908 in connection with the Bullard Professorship in neuropathology in the Harvard Medical School.

Work has been done for five years under this foundation and with the aid of gifts from Dr. W. N. Bullard and Miss Katherine E. Bullard. A list of papers published during these five years (1904–1908) is appended as Number XIV. of the 1908 series.

The work has further been aided by donations from a fund established by the late Arthur W. Blake, which have served to defray a part of the expenses of research in encephalitis, especially embodied in 1904 VIII., 1905 VI., 1906–7 II.

The Proctor Fund of Harvard University has made possible a number of pieces of work, especially that in immunity and anaphylaxis, 1906–7 IV., 1906–7 VIII., 1906–7 IX., 1906–7 X., 1908 VI.–IX., a part of that embodied in 1908 XI., and that of 1908 XII.

The courtesy of the Danvers Hospital trustees and the Superintendent, Dr. Charles W. Page, has permitted an extension of the neuropathological work to include psychiatry. The maintenance of a complete pathological laboratory with adequate assistance and the permission accorded to several workers to use the laboratory privileges form unusual and commendable features in the policy of a State Insane Hospital. The greater part of the results of the Danvers work is not yet published. 1904 VI., 1904 VII., 1905 VIII., 1906-7 III., 1906-7 V., 1906-7 VI., 1908 I., 1908 II., 1908 III., 1908 IV., 1908 X., 1908 XI., 1908 XII., are the chief papers as yet published from Danvers Insane Hospital material. All the earlier work and some of the later work by Gay and Southard on anaphylaxis has been done at Danvers.

The technical work has been done in part at Danvers, in part in the Pathological Laboratory of the Harvard Medical School.

A committee composed of Drs. W. T. Councilman, J. J. Putnam, F. B. Mallory, W. N. Bullard, and E. E. Southard has had general charge of the work.

CYST OF DURA MATER OCCUPYING THE LEFT MIDDLE CRANIAL FOSSA, ASSOCIATED WITH ANOMALOUS DEVELOPMENT OF THE LEFT SUPERIOR TEMPORAL GYRUS.

By JAMES B. AYER, JR., M. D.
(*From the Pathological Laboratory of the Danvers Insane Hospital.*)

Reprinted from
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By JAMES B. AYER, JR., M. D.

(*From the Pathological Laboratory of the Danvers Insane Hospital.*)

I. Introduction.

The present report deals with a peculiar lesion of the dura mater found at autopsy in an aged man. This lesion, unsuspected during the patient's life, was a cyst in the dura mater of the left middle fossa. Despite the absence of related symptoms during life, the condition is regarded by the writer as congenital. The paper deals, on the one hand, with the possible nature of the apparently unique cystic lesion and discusses, on the other hand, its peculiar effect upon adjacent nerve tissue. Wholly quiescent at the time of its discovery, the cyst had effected displacement of the tip of the left temporal lobe which was accompanied by a remarkable thinning of a part of the superior temporal convolution on the side of the lesion. This thinning of the superior temporal convolution is the more remarkable because the intervening convolutions (second and third) remain intact. Thus, if the thinned convolution is in any way due to pressure by the dural cyst, that pressure must have been exerted at some distance. This circumstance, if proved, would tend to show that convolutions differ in their capacity to resist pressure. Convolutional variations of this character have much to support them à priori; but little absolutely convincing evidence exists on the point.

II. Clinical History.

J. L. S., a man, aged 85, native of Massachusetts, single, was admitted to the Danvers Insane Hospital September 8, 1905.

There was obtained nothing of importance in his previous history or habits. One brother was insane for a number of years.

The Record at Entrance.—The patient had done little work for the past fifteen years. For the last four years before admission hearing had been poor, and for three years eyesight had failed. Always considered odd and stubborn, he had for the past three years developed a habit of running out onto the streets thinly clad and losing himself. He had a period of confusion for a long time when he was unable to find his way about the house. His speech was thick for a while, improved, but has had repetitions. Memory has become very poor; he is now untidy and indifferent. Has had several falls, after which he is found lying on the floor.

Examination shows a feeble old man, fairly developed and nourished. There are dulness and moist crepitant rales at bases of both lungs behind. Heart is slightly enlarged. Sounds are irregular, no murmurs. The tension of the radial arteries is increased, and all the palpable arteries are markedly sclerosed. There is edema of feet and ankles. Urine shows few hyaline casts with cells and granules adherent, but no albumin.

No paralyses noted. There is a gross tremor of hands and tongue. Patient unable to stand in Romberg's position. He is almost blind and deaf. Reflexes almost normal. Sensations not markedly disturbed. Four days after entrance he answered relevantly when questions were understood.

January 10, 1906. "Patient has been confined to bed since last note, and has shown practically no change in his mental condition. For the larger part of the time he has remained quietly in bed. He appeared as well as usual yesterday, and died suddenly during the night."

Diagnosis.—"Senile Arteriosclerosis."

Summary.—An old man, one of whose brothers is insane, gradually develops an inaptitude for work, failing in vision and hearing, and showing a loss of memory. He has had a period of confusion, occasional thickness of speech and, just before admission, several falls. Examination shows marked sclerosis of all palpable arteries and an affection of the bases of both lungs behind. Mentally dull.

III. Autopsy.

Anatomical Diagnoses.—Dr. E. E. Southard.

General arteriosclerosis.

Chronic fibrous myocarditis.

Slight mitral sclerosis.
Calcification of aortic valve.
Emphysema and edema of lung.
Hypostatic pneumonia.
Lymphatic cysts of intestinal wall.
Congenital cysts of kidney.
Double hydrocele with chronic periorchitis.
Aneurysmal dilatation of common iliac arteries, and of right vertebral and basilar.
Absence of diploë.
Chronic adhesive pachymeningitis.
Cyst of dura mater.
Edema and pigmentation of cerebral cortex.
Chronic leptomeningitis.
Congenital hypoplasia (?) of left temporal lobe.
Lung shows streptococcus pyogenes in pure culture.

Examination of the Head.—" Scalp normal. Calvarium shows little diploë. Dura inseparably adherent to vault. Sinuses contain fluid blood. The floor of the middle fossa of the skull on the left side is occupied by a flat sac-like fibrous bag, formed by a cleft in the dura mater. The dura mater strips readily from the temporal bone and from the Gasserian ganglion beneath. There are no interadhesions of sac and overlying pia mater. The sac is lens-shaped, with walls a little thinner than the dura mater of the opposite middle fossa, used for comparison, and contains about 10 cc. of slightly opalescent liquid. The inner lining of the cyst is smooth, but shows a few smooth trabeculae near the periphery. The gross appearance of the inner lining recalls that of the venous sinuses of the skull after withdrawal of blood. There is no free communication between the cyst and surrounding cavities, and the cyst was readily dissected out intact. At one point in the outer wall is a focus of recent hemorrhages and laking of blood occupying an area 1.5 cm. square. Along the inner wall is a linear collection of glistening flakes of miliary or slightly larger size, occupying a space 2 x .5 cm. Dura elsewhere normal. Arachnoidal villi moderately developed. Pia mater thickened and hazy, particularly over upper and anterior surface. The left frontal pole shows the most extensive pial thickening.

The pia of the mesial and inferior surface of the brain is almost normal in thickness and appearance. No thickening or other lesion can be noted over the tip of the left temporal lobe . . . . The left temporal lobe is shorter, flatter and more blunt than the right. The absence of material corresponds with the dimensions of the cyst of dura mater mentioned above. The sulcation of the region corresponds roughly with that of the other side. There is no tendency to microgyria. After removal of pieces for histological examination the brain was placed en masse in formalin."

Miscroscopic.—Cerebral cortex, right and left, frontal region: Increase of neuroglia cells in white matter. Pigmentation of nerve cells, neuroglia and adventitial cells is generally marked.

Ascending frontal: In places a decrease of Betz cells, and generally an increase in neuroglia cells, especially along vessels, where considerable pigmentation of glia and adventitial cells is noticeable.

Left calcarine: Pigmentation of glia cells, but not of nerve cells. Increased number of satellite cells and of cells in the outer layer.

Right calcarine: Relative increase in number of vessels in white matter.

Spinal cord shows a mild grade of stationary fibrillar gliosis of the posterior columns. The anterior spinal arteries in all levels examined show reduplication of the elastic membrane.

IV. Examination of the Brain.

It was perfectly evident at autopsy and in the hardened specimen that there was loss of brain substance, but just what part and how much was gone was not at first clear. A careful examination was therefore made to determine in what respect the left temporal lobe was smaller than the right.

On the left, the hippocampal gyrus extended anteriorly about 2 cm. less than on the right, and was somewhat depressed; but the breadth seemed increased. On section the convolutions of the cornu Ammonis appeared somewhat simplified and its anterior-posterior length was markedly shortened, being 2.0 cm. on the left, and 2.8 cm. on the right.

The amygdala was nearly equal in size on the two sides, 1.0 cm. on left, 1.2 cm. on right, anterior-posterior diameter. On the left side, however, there was evidently a considerable dilatation of the ventricle, which separated the amygdala from the dentate lobe by 3 to 5 mm.

The third and second temporal convolutions, while of course not showing normal gyrations, seemed not to have lost much if any substance.

The first temporal convolution, curiously enough, because of its distance from the cyst, showed the greatest change. In the region of the supramarginal gyrus it is of normal appearance, but beginning about the level of the post-central convolution, some 5 cm. from the tip of the temporal lobe, it becomes gradually attenuated until it comes to an end 1 cm. posterior to the tip instead of normally rounding it and entering into its formation.

For microscopic comparison pieces were taken from the first, second, and third temporal gyri and the hippocampal gyrus of each side, and stained according to the following methods: With eosin and methylene blue, with methylene blue, Mallory's connective tissue stain, for elastic tissue, Marchi method for fat, Weigert's myelin sheath stain, for neuroglia with phosphotungstic-acid-haematein.[1]

The hippocampal gyri differed much in gross arrangement of structure. A superficial microscopic examination suggested, however, that there was no great disparity in quantity of nerve cells or fibres, in fat content, or in neuroglia tissue, on the two sides. A thorough study was, however, not made.

Third and second temporal convolutions: Rough measurements showed the cortex on the right to be a very little deeper than the cortex on which the cyst rested. The cell and fibre content of the two sides appeared, however, little different. There was no excess of fat on the left either zonal or in deeper layers, and neuroglia tissue was not greater in amount.

The first temporal gyri, which showed such marked macroscopic differences, were made the subject of a more detailed study. Camera lucida drawings were made of the cortices after the manner of Campbell[2] in methylene blue and Weigert preparations, the conclusions reached being that: (a) The tip (i. e., the present tip) of the first temporal gyrus showed a narrowed cortex with slight deficiency of nerve cells; (b) A short distance from the tip (approximately 2 cm.) the cortices were of equal depth and the nerve fibre content was equal on the two sides or possibly even a little greater on the left, the fibre arrangement being identical.* There was no excess of cortical neuroglia, but rather more fine droplets of fat along the whole circumference on the left. This perhaps is no more than one would expect, for in every place where two cortices came together in the sections studied there was found slight zonal deposits of fat, and it is seen here that the left first temporal gyrus is touched on all sides by cerebral cortex.

In most of the sections a greater or less amount of endarteritis was evident, and fat in small droplets was common in the walls of, and about, capillaries and small blood-vessels.

One small encapsulated point of hæmorrhage was found in the white matter of the superior right parietal region.

Description of Cyst.—Outer wall is old but thin fibrous tissue, showing no active cell process. The inner wall, however, is lined by large-celled connective tissue, the nuclei large and prominent, the fibrils deeply staining with eosin.

No echinococcal hooklets.

Chemical examination of the cyst contents showed a substance soluble in ether, probably either cholesterin or fat.

Summary of Findings.—A cyst of the dura mater, either congenital or of long standing, has caused distortion of growth of the left temporal lobe and neighboring structures, with partial aplasia of the left first temporal convolution. Strangely enough the convolution most affected (T_1) does not at any point come in contact with the cyst, and the missing part of the lobe, if present, must have been separated from it by two other convolutions which appear to be structurally almost normal.

V. DISCUSSION OF FINDINGS.

Four interesting questions are brought out by the autopsy findings:

1. Is the cyst congenital or was it acquired during life?

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* Unfortunately the difference in fixing for the two methods here employed made it impossible to obtain cell and fibre pictures from adjacent sections.

2. Consequent on 1, is the small size of the first temporal convolution accounted for by hypoplasia or atrophy?

3. Why is the first temporal convolution so unduly affected by "pressure at a distance"?

4. What are the bearings regarding cerebral localization?

1. *Origin of Cyst.*—I have been unable to find in the literature descriptions of cysts comparable with the above. Most of the cysts mentioned are not in the dura mater at all, and are generally readily recognized as due to blood extravasation or to echinococcus, in the second of which conditions multiplicity is likely; so that conclusions with regard to this cyst will have to be derived without analogous cases.

With regard to the origin of the cyst:

(a) In favor of its being congenital, we find that the cyst is nowhere strongly adherent but may be stripped out, that there is no external or internal pachymeningitis, that the cortex of the temporal lobe is either normal or shows evidence rather of hypoplasia than of atrophy.

(b) Against its being congenital, there is microscopic evidence of an active process on the internal wall, there is chemical evidence of a chronic process; no mention is made of indentation of the temporal fossa, which might be expected if congenital, and etiologically it would seem to be a more likely location for an encapsulated hæmorrhage than for a congenital cyst.

We are therefore unable to state definitely the origin of the cyst, but think the origin may well have been congenital, and that it was subsequently the seat of slight internal inflammation.

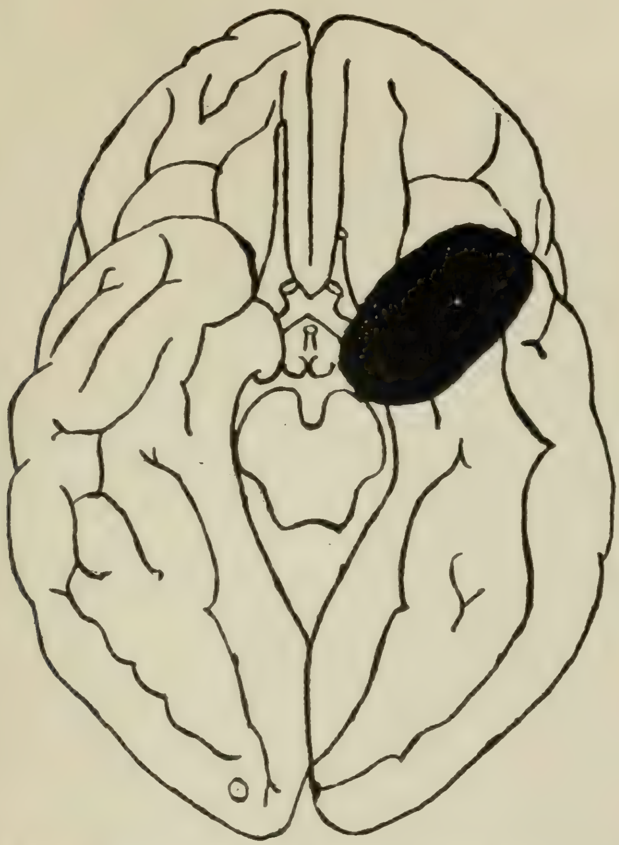
2. *Is the First Temporal Gyrus Atrophic or Hypoplastic?*—There is no evidence macroscopic or microscopic, existing at the time of death, to favor the theory that the cortex has atrophied because of pressure. On the contrary the portion of the cortex which would be expected to show the greatest change, i. e. the region underlying the cyst, appears nearly or quite normal, whereas 2 cm. distant from the cause of pressure brain tissue is missing. (Other possible causes explaining the condition of T_1 may be adduced, but seem altogether unlikely in the presence of such a definite cause as the cyst.)

Putting considerations Nos. 1 and 2 together, *the evidence most favors a congenital cyst associated with cortical hypoplasia.*

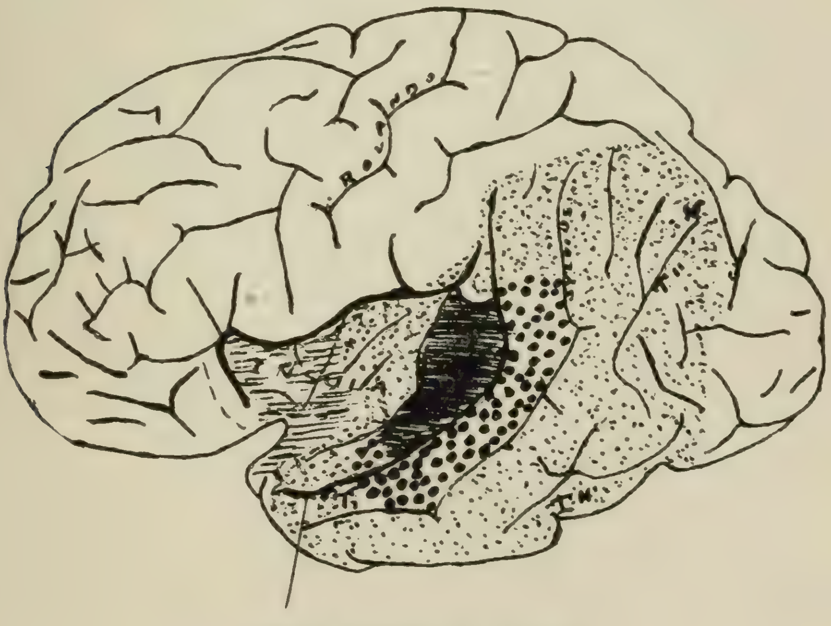
3. *What is the Cause of "Pressure Hypoplasia at a Distance"*?—The answer would seem to be that the character of the first temporal convolution must be different from that of adjacent tissue; it would seem either that the circulation was defective (which does not appear to be the case), or that the chemical or aqueous composition of T_1 was more susceptible to pressure changes than that of T_2 or T_3. It is hard to realize that pressure exerted through a mass, 80 per cent of which is water, should not be equally distributed and equally destructive to all brain tissue.

4. *Problem of Cerebral Localization.*—Campbell[3] found five cases[4 5 6 7 8] where involvement of the left temporal lobe seemed associated with one or another form of deafness, but in these cases the lesions were invariably widespread and consequently no minute localization was possible. Whipham[9] also reports a similar case. After careful histological study, and assisted by these pathological data, as also by some experimental evidence, Campbell describes three types of temporal cortex: (a) audito-sensory; (b) audito-psychic; (c) common temporal cortex. As is seen by the accompanying tracing the anterior third of the first temporal gyrus is designated under "common temporal cortex"; this being so, we should hardly expect its absence in this case to give much if any sensory disturbance. Turning to the history of our case we find that he had been deaf for four years previous to death; if then we could establish the fact that the cyst and consequently the hypoplasia of the first temporal convolution were congenital, it would be a point against the special auditory function of the anterior third of this gyrus. Suppose, on the other hand, the cyst and consequent atrophy of the first temporal gyrus appeared four years before death, we then may think of the "special function" of this part of the temporal lobe.

A case[10] in some ways resembling this one may here be recorded: A tumor of the dura which "seemed to be sarcomatous," about the size of a hen's egg, was found to have made a deep impression in the right temporal-sphenoidal lobe (i. e., the tumor was of the same size and pressed on the same area as in our case, but on the *right* side). The patient was epileptic for nine years; beyond that no motor or sensory symptoms could be detected.



THE SHADED AREA REPRESENTS THE APPROXIMATE POSITION OF THE CYST.
(Tracing from Cunningham's Anatomy, p. 520.)



LOWER BORDER OF SYLVIUS.

Adapted from Campbell's, p. 158.

(a) Audito-sensory (densely shaded)—confined to two transverse temporal gyri and not extending onto insula.
(b) Audito-psychic (large dots)—on free surface of post. 3/5 of T_1.
(c) Common temporal cortex (small dots).

CONCLUSIONS.

1. A cyst of the dura mater, probably congenital, occupies a considerable part of the left middle cranial fossa.

2. Associated with the dural cyst is distortion of the greater part of the left temporal lobe. There is also considerable loss of substance of the anterior part of the superior temporal convolution, presumably from pressure exerted through intervening tissue.

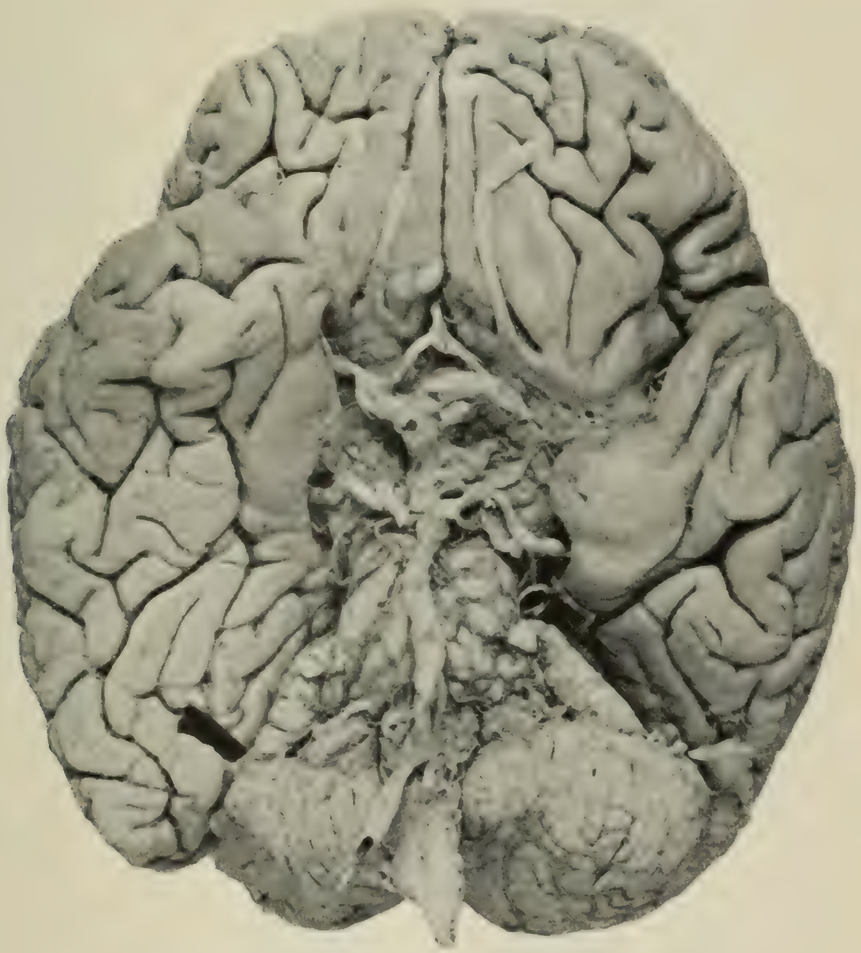
3. Assuming the cyst to be congenital, this condition of the superior temporal convolution may be looked upon as due to hypoplasia.

4. The patient's history gave no ground for suspecting a focal lesion involving the left temporal lobe; nor can the peculiar distortion and hypoplasia of the temporal cortex here described reasonably be related with the clinical history of four years' deafness.

NOTE.—The above report is from the Pathological Laboratory of the Danvers (Mass.) Insane Hospital, in connection with a fourth year elective course at the Harvard Medical School, under Dr. E. E. Southard, for whose kindly assistance the author wishes to express his gratitude.

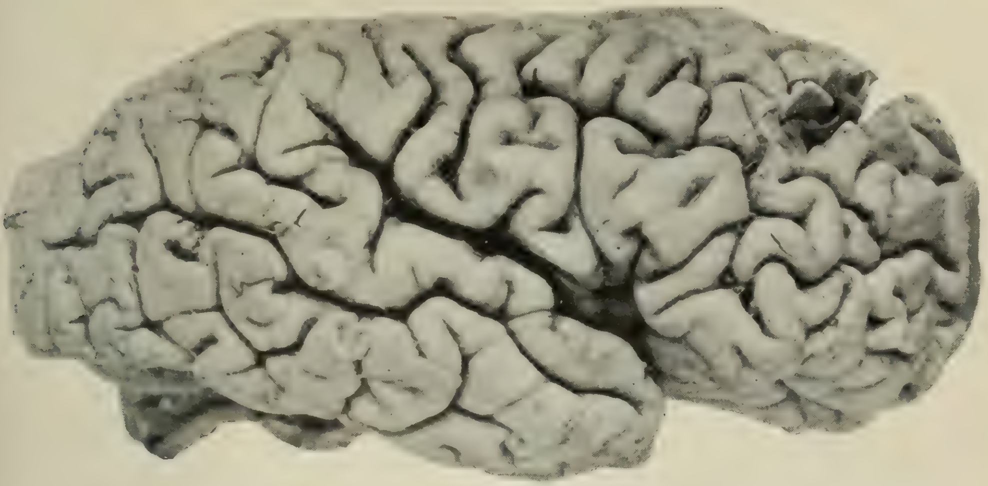
REFERENCES.

1. Mallory and Wright: Pathological Technique.
2. A. W. Campbell: Localization of Cerebral Function, 1905.
3. Ibid., p. 163.
4. Serieux and Mignot: Neurolog. Centralbl., 1901, p. 495.
5. Wernicke and Friedlaender: Fortschr. der Med., 1883, I, p. 177.
6. A. Pick: Arch. f. Psychiatrie, 1891, II, p. 912.
7. C. K. Mills: Brain, 1891, p. 465.
8. Anton: Arch. f. Psychiatrie, 1899, p. 108.
9. Whipham: Lancet, 1881, p. 297.
10. A. Bruce: Trans. Med.-Chir. Soc. Edinb., 1882-3, p. 101.

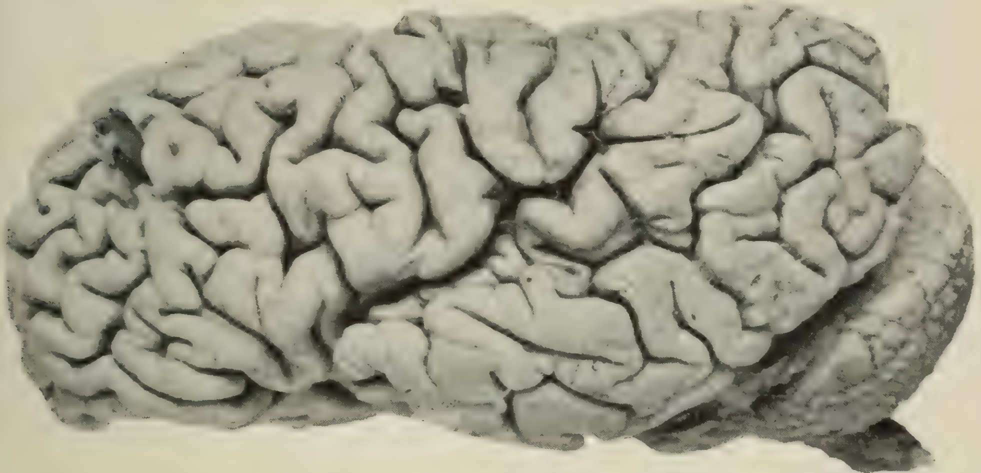


Photograph of the Formaline-Hardened Brain.

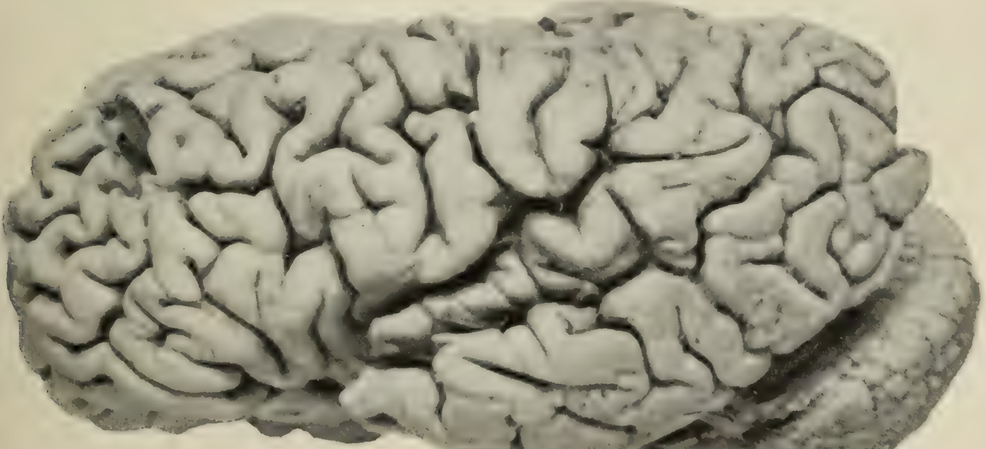
(Cyst occupied a position approximately as shown by diagram in text.)



Right Side, TT_1 Normal.



Left Side, Tip of TT_1 Attenuated and Almost Hidden from Sight by Overlapping Gyri.



Left Side, TT_1 Separated from Surrounding Convolutions by Artificial Means.

ON THE MECHANISM OF GLIOSIS IN ACQUIRED EPILEPSY.

By E. E. SOUTHARD, M. D.,

Assistant Professor of Neuropathology in the Harvard Medical School and Pathologist to The Danvers Insane Hospital.

(From the Laboratory of the Danvers Insane Hospital.)

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The present paper undertakes to describe the histology of certain cases of epilepsy from a functional point of view. The essential novelty of this description consists in the emphasis laid upon certain mechanical characters of the central nervous tissue in disease. The resulting theory might, perhaps, be termed briefly a microphysical theory, in the sense that it seeks a logical basis for the epileptic discharge in certain intimate alterations of pressure in the central tissues. But the term microphysical, besides being a little pretentious in view of our dense ignorance of the nature of nerve impulse, is also too narrow in view of further interpretation. That is to say, however convincing the data in the group chosen—late epilepsies—may appear, the structural considerations which develop are analogous and not identical with conditions in epilepsy at large.

The present study, whether it be termed microphysical, cytological, or what not, lays the emphasis no longer upon characters of nerve fibres or of nerve cells or perhaps of their adnexa. The essay would rather call attention to certain pericellular conditions, giving rise to intimate alterations of pressure. At the present time we can merely describe these conditions and leave their translation into terms of volume energy and of surface energy to the future.

The endeavor to describe pericellular conditions along these lines seems to be in a direct logical line with modern physiological work. No one has brought out more clearly than Sherrington the importance of what happens at the confines of the neurones, the *synapses,*[1] or (perhaps still more happily) the interneuronal *surfaces of separation.*

At these interneuronal or, more broadly, intercellular surfaces of separation a wealth of reaction is possible. A somewhat formidable list of their possible activities is offered by Sherrington. Thus they "might restrain diffusion, bank up osmotic pressure, restrict the movement of ions, accumulate electric changes, support a double electric layer, alter in shape and surface-tension with changes in difference of potential, alter in difference of potential with changes in surface-tension or in shape, or intervene as a membrane between dilute solutions of electrolytes of different concentration or colloidal suspensions with different sign of charge."[2] All this is perhaps as unknown as it is tantalizing; but it cannot be denied that histology can play some part in describing alterations which affect these crucial surfaces of separation, and so lay a foundation for future physical interpretation. Therefore, although modern interest in the synapse or physical surface of separation between neurones has been a physiological interest, the histologist must certainly enter the field, and define carefully what are the types of structural alteration in pericellular and intercellular regions.

Before describing the cases which underlie this study, let us briefly review, in the light of the considerations sketched above, some of the dominant hypotheses in the field of epilepsy.

Since the cases which form the immediate basis of this report are cases of late epilepsy, in which there is no proof of hereditary antecedents, it will be necessary to include in our review the general subject of organic epilepsy. Indeed, inasmuch as our argument hangs upon the possibility of parallel conditions in organic and in so-called essential epilepsy, it is important to bring out the part played by organic cases in the pathology of epilepsy.

The point of view of Hughlings Jackson has been chosen for the first consideration, both because these ideas underlie a somewhat large portion of modern work and because they are free from fashionable and perhaps perverse distinctions between the so-called structural and the so-called functional. After a review of the Jacksonian positions, a number of later contributions will be very briefly taken up.

The service of Hughlings Jackson to epilepsy consists, not merely in the definition of the cortical or partial epilepsy usually termed Jacksonian, but also in the suggestion of general principles of use in the definition of genuine epilepsy. There remains much that is physiologically sound in the *three-level theory* of Hughlings Jackson as applied to the nervous system at large; and the paroxysmal *discharge in the highest level* amongst nerve centers as the physiological basis of genuine epilepsy must stand as an important suggestion for the pathogenesis of epilepsy.

The ideas of Hughlings Jackson as particularly applied to epilepsy have been given expression by a writer in Tuke's Dictionary of Psychological Medicine.[3] Anderson here maintains that there may be an epilepsy taking rise in the lowest nervous level, i. e. the spinal system together with its upward prolongation as far as the oculomotor nuclei. This *lowest level epilepsy* is exemplified in the respiratory or "inward" fits of children. The spasmodic bulbar disease of children, laryngismus stridulus, belongs to the same group. Anderson is inclined to include spasmodic asthma in the adult as an affection of this group showing bulbar instability.

The *middle level* of Hughlings Jackson is concerned with more frequent and definite epileptic phenomena, those, namely, of the partial type named Jacksonian. The limits of the middle level have never been laid down with exactitude. The middle level includes the corpora striata and the motor area of the cerebral cortex as well as much of the sensory cortex, but excludes at any rate the prefrontal and occipital parts of the cerebral cortex. Paroxysmal discharging lesions in the middle level produce *epileptiform seizures* which, though they may be accompanied by unconsciousness, have no essential relation to unconsciousness and never begin with it. These seizures are associated with gross cortical lesions, and begin in the midst of clear consciousness with a localized spasm and, spreading in quite definite fashion, lead eventually to unconsciousness. In Jacksonian epilepsy loss of consciousness is an incident merely.

Not so in the case of genuine epilepsy, which is a matter of the highest nervous level and exhibits unconsciousness as the dominant feature. The highest level is situated in the anterior or prefrontal and posterior or occipital regions. These centers form a sensorimotor mechanism and are also the organ of mind—a sensorimotor mechanism, in the sense that they represent movements and impressions in complex combinations, and the organ of mind, in that consciousness arises and declines in connection therewith. The initial unconsciousness of genuine epilepsy is a sign that a discharge has taken place in the highest nervous level. The sequent universal convulsions signify a spread downward of the discharge to lower levels. Even the bulbar part of the lowest nervous level is likely to be affected for a time, but this part of the mechanism recovers first.

As a matter of course the three-level theory of Hughlings Jackson can no longer be accepted bodily. Nevertheless, however much we shift the boundaries of our levels, we must admit that epilepsy as a high-level disease presents many attractions in theory. Moreover, one point stands out clearly as a point to settle. What, after all, is a discharging lesion? Wherein does a discharge in epilepsy differ from a neural discharge of the usual type? These questions appear logically prior to the question, Where do discharging lesions occur?

In the following paragraphs brief mention is made of various contributions to the pathology of epilepsy as bearing on the mechanism of discharge. No regard has been paid to the chronology of the researches cited, nor is any effort at completeness made.

The Jacksonian three-level classification of epilepsies has already suggested how various in site of origin convulsions of this general class may be. From this standpoint the unity of epilepsy may well be called in question. The topographical method of research, successful as it has been in making out the general principles of neurology, has signally failed for epilepsy.

From the topographical point of view we have to consider: (1) the body and fluids at large, (2) the muscles, (3) the peripheral nervous apparatus, (4) the bulbospinal apparatus, (5) superior nerve centers.

1. The body at large and its fluids have been considered from time to time as yielding poisons of secretory or excretory character which give rise to convulsions. Periodicity in production or continuous formation with explosions after accumulation for

various periods have been supposed. Examples of *non-nervous* conditions of alleged importance in epilepsy are the *persistent thymus and status lymphaticus* of Ohlmacher,[4] the *hypoplasia of aorta and great vessels* of various writers, autointoxication or perverted renal secretion (*paroxysmal hypertoxicity* of Voisin and Péron[5]), the *uric acidosis* of Haig, the *carbamic acidosis* of Krainsky,[6] certain *serum properties* of Ceni,[7] and infection of fluids bathing the central nervous system (*neurococcus* of Bra.[8]) Without attempting to appraise the very various values of the above suggestions, we may remark that no one of them yields insight into the method of production of an epileptic convulsion. Experimental work with injections of blood and urine, uric acid, carbamic acid, *neurococci,* has so far yielded little or no information with respect to the mode of production of convulsions. Nevertheless, it is conceivable that histopathological work upon the differential lines indicated in the present essay might yield results, despite the barrenness of the usual pharmacological procedures. The same suggestion obtains for work with the simple convulsions produced by alcohol and absinthe or incidentally in uremia and diabetes.

2. The *muscles,* it would appear, must actually be normal or nearly normal in epilepsy (regarded as a disease showing repeated convulsions). The fatty changes in voluntary and cardiac muscle, described by Mott[9] in the status epilepticus, can scarcely be thought to accompany each attack of convulsions. Mott's interesting finding is obscure, but may indicate the direction in which changes are proceeding in ordinary attacks of epilepsy.

It is within the range of possibility that a kind of epilepsy might be produced by a poison acting directly on muscular substance (for convulsions) and on central tissues (for unconsciousness.) It is possible that twitchings in the death agony are so produced. But the march of convulsions in ordinary epilepsy suggests a higher origin.

The case quoted by Gowers[10] to show the cerebral origin of epilepsy (case of Oebeke[11]) might be again quoted in this direction. The epileptic in question suffered apoplexy and the muscles of the paralyzed side never again shared in the hitherto generalized convulsions.

3. The peripheral and sympathetic nervous system fails to

offer much light on the mechanism of epileptic discharges. Echeverria's suggestion concerning the sympathetic ganglia seems without foundation. The existence of epileptogenous zones in certain cases (compare Hughlings Jackson's case of a "boy who had fits when his head was touched"[12]), and in Brown-Séquard's experimental guinea-pigs[13] (trigeminal distribution), not to mention certain characteristic auræ in epilepsy, suggests that the peripheral nervous system may be profoundly concerned in the initiation of certain fits. The "lowest level" fits of Hughlings Jackson and the "reflex epilepsies" of various writers render it difficult to exclude the thought that various irritations (peripheral or sympathetic) may give rise to convulsions, provided that normal checks and balances be removed from the discharging apparatus. It seems difficult to conceive, however, any possible differentiation of stimulus which could effect through the linkage of several neurones the characteristic convulsions of epilepsy. In any case we are left with no more insight into repetitive convulsions than what we possess for, e. g., strychnine convulsions. A consideration of peripheral nervous conditions leads us to the conclusion that some higher or central provision is necessary for maintaining the motor effects of a given stimulus beyond the normal period and with abnormal force. The inhibition of countercurrents to a given motor discharge must evidently permit the continuance of that discharge until the exhaustion of the discharging cells.

4. Proceeding centralwards, the epileptologist has to consider the *spinal-trigeminal* type of epilepsy as produced experimentally in guinea-pigs and as observed to occur spontaneously in the offspring of the injured animals by Brown-Séquard. The great variation in the site of the effective spinal injuries suggests that the injury may produce or liberate a substance which passes through the cerebrospinal fluid or blood of the guinea-pig to remote parts of the nervous system where the removal of inhibitions may be brought about. The occurrence of repetitive convulsions in the offspring without individual injuries supports this idea, since the chemical products of maternal injury may readily pass through the placenta. The conception of such placental passage is easier to manage than the conception of direct inheritance of injured spinal cords.

A consideration of Brown-Séquard's work consequently shows an epilepsy compounded possibly of two factors: (a) removal of inhibitions in some part of the nervous system by means of a product of the destruction of nerve tissue and (b) an effective stimulus (trigeminal irritation).

The medullary epileptic centers of Nothnagel[14] and Schröder van der Kolk[15] suggest again a *place d'armes* for the removal of inhibitions. The conception of such a center is not beyond the range of reasonableness; but there are as yet no sufficient histological data for arriving at any notion of conditions in these supposed centers.

5. The higher nerve centers are the favorite seat of modern work on epilepsy. Some writers, as Gowers, regard epilepsy as patently a cerebral disease, though of obscure character. It is evident, however, from our review of Hughlings Jackson, that to term a disease cerebral merely is to neglect to specify whether we deal or not with the sensorimotor and psychical mechanism. The cerebral character of epilepsy, were it admitted, carries us a short way only in the analysis.

As a fact the higher centers are certainly the loci of the most extensive and important inhibitions, so that the synaptic tissues of the cerebral cortex in particular are approached with a degree of hope. The satisfaction of this hope along anatomical lines has been considerable. The intimate effects of the gross lesions found—a task of histopathology—have been less easy to decipher. The well-worn and efficacious methods of classical neuropathology—of cerebral and spinal localization—are of less service in these directions, and of almost no service when it comes to the elucidation of non-destructive lesions.

The best effort of classical and localizing neuropathology has been spent on the possible relation of Meynert's sclerosis of the cornu ammonis to epilepsy. As an epileptogenous center the cornu ammonis ranks with Nothnagel's medullary center. The possibility, nay in some cases probability, of association between these centers and epilepsy is certain. The manner of this possible association is not clear. The usual form of critique is to point at cases without such centers and stringently require some unique and disparate center for satisfactory explanation. As a matter of fact the present superficial review indicates that we must probably accept what may be termed a manifold causation for epilepsy. If this is granted, we must evidently seek the intimate mechanism in type cases. The task is to show what may be the basis of the inhibitions necessary for the production of repeated convulsions.

An enumeration of the manifold anatomical causes which have been alleged in epilepsy is almost superfluous—foci of softening in central or temporal cortex, sclerosis of cornu ammonis, gliomata of various regions, dural endotheliomata, calvarial thickenings, chronic leptomeningitis, chronic encephalitis, focal lesions of a chronic inflammatory character (including tubercles and gummata).

So far as those who report these lesions regard them as causative of epilepsy, in the sense that internal capsular hemorrhage is causative of hemiplegia, these modes of explanation seem destined to failure.

Another path is open. In common with several other workers, the present writer feels that the proper mode of explanation must be a cytological one. Conditions at the synapses must be investigated. The methods for studying nerve tracts should be discarded for the present purpose and replaced with finer histological methods.

The histopathologists have worked to some extent in the field of epilepsy. Their findings are usually taken as secondary. Thus Adolf Meyer,[16] in a highly critical review of the pathology of epilepsy, remarks: "Histological findings of the brain yield little that could be called causative. The occasional gliosis of the cortex discovered by Chaslin and Bleuler, and corroborated in some cases by Alzheimer, Weber, and others, and the nuclear changes shown by Bevan Lewis,[17] are not explicable, except as a secondary condition." It is evident that the changes described by Clark and Prout[18] and by Mott[19] are liable to the same charge.

Perhaps we should not throw out of court some of the most precious material for the elucidation of the general problem. The present writer is inclined to think that, by combining the consideration of *gliosis* on the one hand and of certain *stratigraphic changes* on the other, a structural basis can be laid for the understanding of the inhibitory mechanism which underlies epilepsy.

Before inquiring what these significant changes are, it may be well to forestall certain objections.

Thus it may be alleged that the alterations described below, being found in cases of late epilepsy, are not only of suspicious value for any special purpose, but also can obviously have no relation to the problem of idiopathic epilepsy. To the latter objection I may reply that, in the case of idiopathic epilepsy, we are often in the position of some one who had inherited the second generation of Brown-Séquard's guinea-pigs without knowledge of injuries to the first. We are obviously better off if we examine cases of epilepsy whose histories we know, with respect to date, manner of origin, and course. Naturally the conditions of inherited epilepsy are not reproduced with exactitude in these cases; but surely, were we keen enough, we could make out the elements involved in the first instance. And, if it be interposed that the hypothesis of inherited toxines is pure speculation, I reply that, after all, I do not use the hypothesis in interpretation of specimens, and the neglect of cases of epilepsy, just because they show lesions, is an unphilosophical neglect.

But the former part of the objection—viz., that the changes, being found in admittedly organic cases, have little differential value for our purpose—is more serious. To this I would urge that the data of cortex histology are at the present writing not wholly obscure—witness the work of Ramón y Cajal or the work of Campbell.[20] That is to say, there is a certain outstanding stock of knowledge which permits us to say roughly where in the cerebral cortex and *in what layers* certain operations go on. As general topographical relations begin to be understood, there is becoming clear a certain movement in knowledge of a stratigraphical character. And, although the doctrine of inhibition is still inchoate, we are not quite destitute of contributions thereto.

The cerebral cortex is evidently the most promising field for work, since it contains synapses of primary importance. The well-known cases (one of which was cited above) in which hemiplegia supervening in epilepsy suspends convulsions on the paralyzed side throw interest back upon the cortex. Moreover Prus[21] has shown that painting the motor cortex with cocaine will prevent generalized convulsions, although it fails to suspend the electrical irritability of the cortex for single muscular movements.

Now the single muscular movements are, almost beyond doubt, initiated by activity in the characteristic large cells of the precentral region (giant cells or cells of Betz). When cocaine is locally applied to the cortex (or when bromides are administered), we have to suppose either a general or else a differential diminution of irritability in the nerve cells of the cortex. In case this heightened threshold of stimulation is general, then we must suppose that electrical stimulation breaks through more speedily for the great motor cells (perhaps by reason of their relatively extensive receptive surfaces) than for the remainder of the cortex. Or in case the heightened threshold be differential, we may suppose the cocaine or bromide to leave the motor cells unaffected and to act upon the remainder of the synaptic apparatus.

Proceeding to an analysis of the functions of the motor cortex we observe, of course, tremendous gaps in knowledge. In the first place, as taken for granted above, the giant cells must be regarded as analogous to the anterior horn cells of the spinal cord and to the Purkinje cells of the cerebellum, namely, as the discharging elements for that portion of the apparatus to which they pertain. It is, therefore, by means of these cells that some kinds of epilepsy are rendered possible. The remainder of the motor cortex appears to have three possible functions (exclusive of unknown ones)—the *reception* of stimuli from elsewhere, and the modification of motor discharges in one of two directions, either through *inhibition* or through *facilitation* of the discharges. As for the reception of stimuli, we do not stringently require the allotment of a separate type of cell: the receptive surfaces of the motor cells could readily take up energy directly from instreaming fibers (from the postcentral gyrus or elsewhere). The functions of inhibition and facilitation seem to require more specialized apparatus. Most workers assume that these functions are performed by the outer layers (on acount of various evolutionary considerations which do not here concern us). Thus, according to this conception (which is not far removed from the current conception), the motor cells are those elements upon which the remainder of the cortical elements play, checking or hastening their impulses and perhaps modifying their force of impulse.

We considered above that the muscles must in the great majority of epilepsies be normal muscles. Just so with the motor elements and the intervening tracts: as a part of the transmissive apparatus, both spinomuscular neurones and corticospinal neurones must, to permit epilepsy, in the majority of cases be functionally normal. Just as it would be immensely difficult to procure conditions at the surfaces of muscles which would permit a simulation of the epileptic march of contractions from group to group and from limb to limb, so also would it be a complex circumstance which would permit the same event through effects wrought upon the surfaces of the anterior horn cells. Higher in the axis, such generalized disorder becomes more easy to produce, perhaps by reason of the intercalation of the cerebellum and of Monakow's tract.[22] The possibility of a cerebellar type of epilepsy cannot be denied even on clinical evidence. But such types and the bulbar or pontine types of various authors must represent a combination of circumstances greatly less frequent than those cortical conditions which admit epilepsy. And the central phenomena which underlie the epileptic march of convulsions—the "occasional, sudden, rapid, and excessive discharge" of Hughlings Jackson—must happen in these subcortical cases within so small a space as to be extremely difficult to unravel histologically.

We have analytically arrived once more at the cerebral cortex as the most promising field for work. Therein exist the motor cells as so many filters through which the nervous currents are poured. These filters are of a certain capacity, and they become occluded to nervous currents after a time (or so we may express the phenomenon of exhaustion). What now governs the amount and character of the currents which reach the filtering surfaces?

We must be wary of speculation concerning the nature of nerve impulse, at least for the present purpose. What have epileptologists found in the cerebral cortex which might influence the amount and character of impulses to be let through the motor cells?

In the first place, there are certain vague ideas afloat concerning the possible epileptogenous character of variations in intracranial tension. Gowers, in the latter part of his second edition, speaks with a certain ridicule of various trephinings in epilepsy based on these vague ideas. Nevertheless, for fifty years since the carotid compressions of Kussmaul and Tenner,[23] these ideas have had a certain justification. We are able to reconcile these findings in several ways with more special ideas, and in case the Kussmaul-Tenner contractions are not of subcortical origin, we can still invoke the differential action of cerebral anemia upon the various parts and layers of the cortex.

Secondly, epileptologists have busied themselves with local (intracortical) vascular conditions. A revival of conceptions of this group is seen in the latest book on epilepsy accessible to me.[24] Herein J. Turner describes epilepsy as "a disease occurring in persons with a defectively developed nervous system, indicated by certain structural peculiarities, and in whom there is a special tendency to intravascular clotting; the convulsions are a symptom of the disease, and prior to a seizure a condition of cortical stasis is induced by the formation of intravascular coagula." Whereas none will doubt that there are cases of epilepsy based upon intracortical thrombosis, it is probable that Turner's hypothesis is of too general a character to prove satisfactory in the end.

We now approach considerations which it is less easy or desirable to blink, namely, the very general allegation of cortical gliosis in epileptics and the cell-findings of Bevan Lewis and of Clark and Prout.

With respect to gliosis, it was developed above that the condition is usually deemed secondary. The present writer feels that the significance of gliosis in epilepsy may be attacked on another line; the condition is altogether too generally found to permit its unequivocal acceptance as intimately related to epilepsy. Gliosis of a particular character and locus, as will be developed below, may attain a separate and important meaning for epilepsy. The gliosis required is evidently not a gliosis following destruction of motor elements or a gliosis following generalized atrophy, but a gliosis having special relation to the non-discharging part of the motor cortex.

The writer therefore agrees with those writers who allege the frequent or even virtually universal finding of gliosis in cortical epilepsies, but is not satisfied that all of these glioses have been properly localized or interpreted. Especially is this true of the superficial cortical gliosis of many writers; this, the most frequent of significant lesions in the brains of adults, must be quite particularly investigated before accepted as epileptogenous.

The important stratigraphic contributions are those of Bevan Lewis and of Clark and Prout. The second cortical layer is the locus of lesion in both studies, and this unity of opinion is the more remarkable since the later writers (Clark and Prout) do not appear to have considered Bevan Lewis' work as extremely important.

Bevan Lewis [25] described certain cell changes, demonstrable by fresh methods, as characteristic of epilepsy, although found to some degree in alcoholic brain-disease. The characteristic lesion is a degeneration of the small nerve cells of the second cortical layer. The nucleus is first injured and presents in its center a refractile fatty body. Later stages of the injury may show the nucleus occupied by two such bodies, or completely replaced by one. At a stage when one-half of the nucleus is occupied by such a body, the nucleus begins to stain poorly and to be scarcely differentiated from the cell-body. The cells themselves persist for some time. The cells of other layers besides the second are occasionally affected but not universally. The fatty bodies eventually enlarge and burst, leaving the cells strikingly vacuolated. Along with the fatty nuclear change and vacuolation, Bevan Lewis says the " neuroglia is, as long known, invariably in excess of the normal; but there is no increase of adventitial nuclei or of spider-cells."

Parallel with the above changes in idiopathic epilepsy, Bevan Lewis describes certain other findings as characteristic of epileptic idiocy, viz., inflated spheroidal cells with few processes in the same (second cortical) layer.

These stratigraphic lesions of Bevan Lewis suffer from the lack of sufficient indications whence the sections were derived. Moreover, his induction that the sign of the convulsive constitution is a disparity between nucleus and cell-body, with alteration of the nucleus, is over-bold and probably too general.

Turning to Clark and Prout,[26] we find these writers incriminating the same second cortical layer. Curiously enough, these writers again allege characteristic nuclear changes. Most of their work appears to have been done with the motor cortex; but topographical description is for the most part lacking.

Chromatolysis was found by Clark and Prout in all types of cortical cell, most marked in the large pyramidal cells of the third layer. Some cell-bodies stained diffusely; some showed finely granular chromatic substance. The type of chromatolysis varied. Vacuolation attended the chromatolysis.

The nuclei of the cells throughout showed changes, but particularly the nuclei of the small pyramidal cells of the second layer. These nuclei are swollen and granular and often without distinct membrane. In the cells of the third layer, the nuclei are often distorted, small, pale, or have " almost disappeared." The karyoplasmic network of the nucleus was often absent and replaced with a lightly staining granular mass. The nucleolus—and here lodges the most remarkable portion of Clark and Prout's findings—was found displaced to one side, especially in the cells of the second layer. The nucleoli were often abstracted in the line of direction of the knife employed in cutting the sections. More than sixty abstracted nucleoli were found in a section with a surface of one centimeter.

Disregarding certain details of description, the findings of Clark and Prout correspond to those of Bevan Lewis, in so far as they point to the outer portion of the cerebral cortex, and particularly the second cortical layer as the essential locus of disease in epilepsy.

The present writer feels, as the above analysis shows, that the second cortical layer and the intermediate layers are certainly the loci to examine on theoretical grounds, since therein must lie the apparatus for controlling and modifying motor discharges.

In an experience of towards a hundred autopsied cases of epilepsy of many types, the writer has examined both the nervous and the neuroglia structures with greater or less care. The phenomenon of gliosis in the subpial and perivascular regions is so constant as to be at first blush very promising. But this finding proves, if anything, too much; and indeed a sclerosis of greater or less degree is found in so many cases of nervous disease that are not epileptic that little can be induced from the finding with respect to epilepsy. The loss of a certain transmissive or associational function can probably be assumed from this superficial lesion. In passing it may be noted that the topographical analysis of lesions of this stratum, as evidenced by methods for neuroglia, might prove of greater service to mental disease than the more usual analysis by myelin sheath methods. As is well known, the lips and bases of the gyri are more apt to show a dense gliosis than the crowns of the gyri. In epilepsy this finding—which may be significant of difficulty in transmission from gyrus to gyrus—is not particularly striking. On the contrary, I have found rather more often a tendency to stringently focal glioses which are found upon the crowns of the gyri perhaps as often as at the bases. Plate X, Fig. 1, illustrates this finding and exhibits the cortex of the motor area (arm) overlaid with neuroglia fibrillary tissue in three distinct nodules separately by unaffected tissues. Such appearances can be found in numerous brains upon search; in certain cases of organic epilepsy, the finding is practically universal. The similar focal distribution of neuroglia tissue about a cortical vessel from the same case (Plate X, Fig. 2) shows how chary we must be of making functional inductions from findings of this character.

The writer is, therefore, skeptical concerning the significance of subpial gliosis for epilepsy, though seeing therein evidence of a transmissive disorder of great interest topographically in mental disease. This statement seems unconditionally true for the gliosis of uniform depth (or gradually augmenting at bases of convolutions) which is so often seen. And, despite the greater incidence of a more focal type of sclerosis in the writer's cases of organic epilepsy, he is wholly prepared to admit their dependence upon more general conditions than the epileptic discharge. Probably most workers would agree that such findings, if significant, are in any event secondary.

There are glioses of a different order of significance. In connection therewith the following case may be presented. The case is anatomically extraordinary and affords some little color to the well-known cornu ammonis theory of epilepsy. The epilepsy had lasted only nine weeks (although there had been shaking attacks for a year or more), and was ended by a series of convulsions, amounting to status, lasting four days. The autopsy showed intense intracranial congestion with a deep red line in the midst of the right cornu ammonis. Plate XI shows conditions in the cornu: injection, extreme overgrowth of neuroglia cells, from without inwards, *coupled with no demonstrable loss of nerve cells,* except perhaps in the outermost layer.

Before discussion, the details seem worthy of presentation:

Case I.*—The patient, a fisherman, born in 1836, had a number of insane but, so far as could be learned, no epileptic, relatives. Scarlet fever in childhood had left him slightly deaf. There were two accidents with unconsciousness, one a fall from mast-head at 54 or 55 years with unconsciousness three or four hours, the other at 65, unconsciousness from vapor on a launch. A gradual decay of faculties began at 66 years: failure of memory, depressive ideas, train of thought limited to fishing, attacks of trembling without unconsciousness, irritableness. At 68 years nine weeks before death, the patient began to have fits which were at first severe but infrequent (three, once with a slight shock, in the first three weeks), then grew less frequent but remained severe, and ended by four days of practically continuous convulsions with unconsciousness (over 400 attacks). The convulsions were general, clonic, with head and eyes turned to left, right arm flexed over abdomen, thumb drawn under fingers, left hand extended by side. At times there were tonic convulsions.

The autopsy (four hours after death) showed the following conditions:

Intracranial congestion.
Focal encephalitis of right cornu ammonis.
Bronchopneumonia of hypostatic distribution.
Coronary arteriosclerosis with calcification.
Aortic and renal arteriosclerosis.
Chronic valvular endocarditis.
Chronic fibrous myocarditis.
Fatty myocarditis.
Chronic passive congestion of liver and kidneys.
Marked chronic external adhesive pachymeningitis.

Following is a description of findings in the head:

Calvarium not notable. *Dura mater* completely and firmly adherent to calvarium. *Sinuses* negative. Arachnoidal *villi* moderately developed. *Pia mater* dark in color, with veins intensely engorged. Pia mater a little hazy and in the frontal regions distended with liquid. None of the intracranial *arteries* show macroscopic signs of arteriosclerosis. Weight of encephalon 1270 grams. Blood content of cortex high. There are no notable anomalies in size or arrangement of gyri. The gyri are as firm as normal except that the cornu ammonis are a little firmer than usual. Section of the encephalon in various parts shows intense injection of the brain substance affecting both gray and white matter. The right cornu ammonis shows a grayish red linear streak running about the convolution in the nerve-cell layers. This has an anteroposterior extent of perhaps 1 cm.

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* I am obliged to Prof. A. M. Barrett for the material of this case, drawn from his Danvers service.

There is no need for the present purpose of analyzing finely the relationship of symptoms and findings in this case. Probably there exists in the literature no more demonstrative case of a virtually non-destructive lesion of the cornu ammonis which can be reasonably related to an epilepsy which was acute. A focus of irritation existed in the right cornu ammonis which, whatever its cause, exhibited an interstitial accumulation of neuroglia cells leaving the nerve cells intact. It does not require undue stretching of the facts to allege that new and unusual surfaces of separation (to use Sherrington's phrase) had been provided for the nerve cells in question.

Suppose that these cells subserve some sensory function (as that of smell), there is little doubt that a continuous stream of impulses is impinging upon these cells causing them to discharge along their normal lines. Their discharge may occur to the point of exhaustion, or, if not so violent and continuous, the discharges of the next neuronic links may be limited by exhaustion or by counterstreams or intercurrents from other regions. At all events, whatever the details of spread (and those may well be beyond the range of investigation), the elements of an hypothesis stand out and get illustration from the above case: *Fresh surfaces of separation have been interposed between sets of nerve elements.* Those elements which have their currents in the forward direction, being placed under fresh conditions of intimate pressure, initiate continuous or lasting streams of impulse which set the remainder of the apparatus moving in abnormal fashion. Supposing, for the sake of illustration, that these particular intimately compressed cells formerly subserved the sense of smell, it might be inquired whether some unusual and violent olfactory stimulation at the sensory surface might not produce epilepsy. An affirmative reply is wholly permissible acording to the present hypothesis; but the combination of circumstances which would permit such a result is simply unusual. The above case of focal encephalitis of the cornu ammonis may be therefore said to demonstrate clearly but one of many possible chains of events in epilepsy.

Let us now examine a second case of epilepsy which presents somewhat similar features, but which ran a chronic course and falls more readily into the so-called organic group.

Our second case is also one of unilateral cornu ammonis lesion. The symptoms in this case can be traced to an aneurysm of the left anterior choroid artery which compressed both the uncus and the superior temporal gyrus of the left side. It is fortunate that the date of this aneurysm (or at least of a hemorrhage early in the aneurysm's development) can be assigned with considerable exactitude, because the patient was taken to a general hospital at the age of 44 suffering from her original convulsions. Epileptic convulsions of mild character ensued, but there was no marked mental failure for ten years or more. The patient died a confirmed epileptic at the age of 60.

Details of the case follow:

Case II.—M. Y., female, born in 1848. One sister insane. An aunt epileptic. Nine other brothers and sisters without history of insanity. Education poor. Mental capacity good. Married at eighteen years of age. Gave birth to five healthy children. At the age of 44, she was brought to a general hospital having "fallen in a fit" and vomited in the street. Respiration of Cheyne-Stokes' type. Pulse fair strength and volume, regular. Right external strabismus. Right pupil dilated and stationary to light. "Chewing motion of jaws." Before nightfall the next day she became rational and could answer questions tardily. Semiconsciousness was maintained without change of symptoms for twenty-four days, whereupon a sudden attack of nausea and vomiting with cyanosis and slight twitching of arms supervened. She grew gradually brighter during the next fortnight but afterwards, about seven weeks after the original admission to hospital, began to complain of a numbness in the right hand. Her general condition gradually improved and she was discharged nine weeks after her accident much relieved.

After this attack the patient had frequent slight epileptic convulsions, affecting the right side. Her mental power gradually failed. Failure began to be particularly extensive at the age of 55. The patient developed visual hallucinations at 60 years of age and grew gradually worse until she became confined to bed eight days after admission to an insane hospital.

A somewhat unusual array of skin lesions was presented suggesting decubitus in some ways, but far more extensive than usual. The left foot was greatly swollen and blistered. The pupils were equal. The right pupil was stationary to light. Sensation, as far as demonstrable, good. Knee-jerks and Achilles reactions brisk, on both sides. Brisk Babinsky reaction on right side. Plantar reaction absent on left side. Elbow and forearm reflexes exaggerated. Abdominal reflexes normal.

Organic reflexes impaired. General muscular weakness with incoordination and inability to stand or walk. The patient's utterances were confined to a few oaths.

The patient showed no convulsions while in the hospital and died two days after admission.*

The autopsy (seventeen hours after death) showed the following conditions:

Multiple ulcers of skin (decubitus?).

Fatty change of heart muscle.

Chronic diffuse nephritis.

Slight aortic sclerosis.

Mitral and aortic valvular sclerosis.

Bilateral hypostatic pneumonia.

Chronic adhesive pleuritis of left apex.

Chronic splenitis.

Slight chronic external adhesive pachymeningitis.

Chronic internal hemorrhagic pachymeningitis of vertex in both hemispheres.

Dilatation of lateral ventricles of brain.

Flattening of convolutions.

Focal basilar arteriosclerosis.

Aneurysm of left anterior choroid artery with atrophy of left uncus and compression of superior temporal gyrus.

Herniation of lips of superior temporal gyri.

Dilated perivascular spaces of left basal ganglia.

General encephalomalacia and myelomalacia?

Following is a description of findings in the head:

Hair red, mixed with gray. *Scalp* more adherent than usual to calvarium. *Calvarium* contains a moderate amount of diplœ. *Dura mater* slightly adherent to calvarium in vertex region, but more than normally adherent to base of skull especially in middle fossæ. The bone underlying this region of adhesion is slightly porous. The inner surface of the dura mater on both sides over the vertex and superior surface of the cerebrum is underlaid by a delicate transparent slightly brownish membrane measuring nowhere over 1 to 2 mm. in thickness and playing out gradually over the flanks of the brain. *Sinuses* normal. *Arachnoidal villi* moderately developed. *Pia mater* everywhere transparent and clear except over both hippocampal gyri and the tip of the left temporal lobe. The pia mater is everywhere distended by the swollen brain and contains very little liquid. The cisternæ at the base contain considerable slightly turbid liquid. *Brain weight* 1165 grams. Convolutions flattened notably on left side. The cortical surface suggests a moderate pigmentation. The gyri show a normal arrangement and size, in both hemispheres, except for distortion of the left temporal gyri opposite the optic chiasm. This latter process is merely incidental to the distortion of structures consequent upon an aneurysm imbedded in tissue below the left uncus. The aneurysm is globular and measures 1.8 cm. in all directions. The cavity of the dilated vessel is completely filled with laminated clot. The wall is of varying thickness, measuring internally, where its surface gives directly upon interpeduncular space, from 3 to 4 mm. deep. The remainder of the wall also varies in thickness but rarely exceeds 2 to 3 mm. in depth. The interior of the aneurysm shows chocolate-colored clot peripherally with mixed red and gray clot in the middle. The vessel affected is the anterior choroid artery. The proximal portion of the artery shows in common with the internal carotid and Sylvian arteries in this region a considerable thickening and dilatation so that the aneurysm appears to be situate upon a kind of yellow stem measuring 1 cm. in diameter. The other arteries at base show well-marked focal sclerosis without dilatation except in the case of the left posterior communicating artery which is dilated to a diameter of 2 mm. and runs in the same axis with the posterior cerebral artery.

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* I am obliged to Dr. H. A. Cotton for these notes, drawn from the records of his Danvers service.

The substance of the uncus appears to have been largely destroyed by the aneurysm, but remains of it, together with a portion of the superior temporal gyrus, can be made out in that portion of the brain substance which has been displaced outward and downward by the lesion. The substance of the left putamen, external capsule, claustrum and white matter of the temporal lobe contains numerous dilated perivascular spaces. The lenticular nucleus has been displaced outward and upward but appears to have undergone no diminution in size. The internal capsule has apparently not suffered in width.

The contour of the ventricles appears to be slightly altered by pressure. Frontal section in a plane 1 cm. posterior to the optic chiasm gives the following measurements:

Left lateral ventricle—body 2 cm. laterally × 0.9 cm. from above downwards.

Left lateral ventricle—inferior cornu 2 × 0.8.

Right lateral ventricle—body 2.3 cm. laterally × 0.5 cm. from above downwards.

Right lateral ventricle inferior cornu 1.2 × 3 cm. laterally.

These measurements appear to show that, whereas, both ventricles are moderately dilated, the lateral ventricle on the side of the lesion is somewhat more dilated than its fellow. It is possible that this condition is related with alterations of pressure in the area supplied by the anterior choroid area. Another hypothesis is that the lesion has compressed the foramen of Monro.

The convolutions although flattened are reduced in size and almost of plastic consistence. This character is shared by the cerebellum, pons, bulb and spinal cord. No focal lesions were seen elsewhere about the aneurysm.

The tissues of a case of sixteen years' standing cannot afford the striking evidence of acute change which was afforded by

Case I. A different sort of evidence is procurable. I have chosen for photographic reproduction the superior temporal gyrus, because that gyrus seems to have suffered most recently from the effects of pressure (Plate XII).

The photograph shows several points of interest. The normal depth of cortex is well maintained. The innermost layers of cortex are not far removed from normal, exhibiting a few trifling denuded areas. On the other hand, the outer nerve-cell layers exhibit a relatively striking irregular denudation of nerve cells. The second cortical layer is notably cut through at one point by a lane virtually bare of the characteristic small nerve cells. And the layer of large external pyramids has preserved but two islets of its characteristic cells. Under the stress of a somewhat diffuse pressure, coupled no doubt with arterial changes, the temporal cortex has become somewhat irregularly denuded of a portion of its cells, and these rather in the outer layers. *The larger cells tend to last longest; the smaller cells* (particularly of the second and third cortical layers) *tend to disappear first.*

It is unnecessary here to linger on this point which becomes clearer with later cases. I would only insist that not only does inhibition (or hastening action) on the part of these outer layers become more difficult through the absence of whole blocks of cells, but also any impulse once initiated in a process of some intact nerve cell gets a diminishing chance of interruption by countercurrents of any sort. There is a kind of functional vicious circle in tissues subject to these differential lesions. There is a kind of inertia in impulses once set going. Intercurrences are few in this new synaptic tissue of lowered quality. The multitude of energy-absorbers which formerly enwrapped the path of a propagating impulse has now vanished. The system is much simplified; and, until such time as the onset of atrophy shall separate the discharging constellations altogether, it would appear that immediate discharges can scarcely be stopped among surviving cells, when they are stimulated.

The present case showed conditions of this sort in all the convolutions abutting upon the aneurysm, and, indeed, slight tendencies in the direction of differential cell atrophy were observable throughout the brain (perhaps the result of chronic internal hydrocephalus). Such tissues, intermediate between perfect tissues and thoroughly atrophic ones, form the proper soil for keeping up, if not for producing, epileptic discharges.

In Case I we were fortunate enough to light upon an adequate epileptogenic focus in the form of a localized encephalitis in one cornu ammonis. In Case II we again meet with a lesion in one cornu ammonis which may well have formed an epileptogenic focus in the first instance and subsequently formed new ones in the course of its gradual and differential destruction of tissues. In the second case the original focus has doubtless wholly vanished with the growth of the aneurysm. All we now find is a medium favorable for unimpeded discharge. The recent active foci may have escaped search; or an epileptic habit may have developed, by virtue of which occasional summations of stimuli from several sources may serve to set off the chain of convulsions.

We now turn to the more debatable ground of those organic cases in which the direct relation of lesions to symptoms is more difficult to prove largely through the multiplicity of the lesions. (1) By means of Cases III and IV I hope to lend further support to the ideas developed from Case II—viz., to set forth more clearly the conception that tissue destruction of moderate degree may frequently leave the discharging apparatus intact, whereas the inhibitory and controlling apparatus is destroyed. We shall find that even coarsely destructive lesions of the motor cortex are prone to this differential effect and that, whether for evolutionary reasons or not, the more delicate portion of the machinery is first lost. (2) Finally in the residue of cases described I hope to develop further the idea of unchecked discharge and a related conception, that of progressive or lateral discharge.

Plates XIII and XIV (from the right precentral and right occipital regions of Case III) show clearly one point: the preservation of large elements and simultaneous disappearance of small elements about small infarcts, Plate XIII shows this tissue property most distinctly, because the confusing feature of neuroglia cell overgrowth has passed. The lesion in Plate XIII is possibly far older than that shown in Plate XIV. In both instances, however, there are lanes of nerve-cell destruction setting in from the exterior. Along the borders of both lanes the larger elements are still in evidence. At the right side of both plates it is evident that the second cortical layer and (to some extent) the third have been destroyed, so that underlying elements are in so far without their influence. At the same time these larger elements (as adjacent sections prepared according to Benda's method show) are now well wrapped with neuroglia (in a quiescent state in the precentral region, in an active proliferating condition in the occipital region).

Plate XIII betrays the stratigraphy of the cortex particularly well with respect to the differential loss of elements of which we are speaking. The outer nerve-cell layers tend, so to say, to weather out more readily than do the inner layers when under virtually the same conditions with respect to noxious agent (in this case ischemia). And, although infarction leaves at times many bizarre figures of differential destruction, yet the configuration of layers seen in Plate XIII occurs very frequently in organic cases.

Plate XV (from another case, Case IV) illustrates the same tendency in diffuse atrophy. Again a section is chosen from tissue which is no longer undergoing active neuroglia proliferation, so that the preservation of numerous large elements is manifest together with a loss of many smaller elements. This appears to be true throughout all the layers; but the outer layers have suffered maximally. Notably in the middle of the layer of moderate-sized pyramids, in the midst of a general destruction of all other nervous elements, a single nerve cell of good size remains. The Benda preparation from the adjacent section shows this self-same isolated cell surrounded by the fibrillar neuroglia of the little infarct in which it lies. We cannot doubt both that this cell has lost touch with innumerable streams of impulse from without and that also a new surface of separation has been provided for any impulses that may reach the cell.

Under such circumstances not only are the cells divorced from normal controls but they are placed under peculiarly good conditions for direct irritation or for activity engendered by direct pressure.

The details of these two cases follow:

Case III.—G. C., male, born 1840, of average capacity, had a "sunstroke" in the Civil War, and about 1876, while working as customs inspector, had a severe attack of convulsions, which confined him to bed for two or three weeks. There were then no convulsions for several months: but then they recurred and increased in frequency, occurring both at night and during the day, until about 1902. Delirious episodes. Increasing dementia. Unruly. Sent to Soldier's Home, 1903. Incapacitated for work since 1886. Evidence of mental failure since about 1880. Admitted to hospital April 11, Died June 20, 1906. Marked insane heredity.

The autopsy (twelve hours after death) showed the following conditions:

General arteriosclerosis (aortic, coronary, splenic, renal, cerebral, iliac, with some gross changes in all large arteries examined). Calcification in aorta and internal iliac arteries.

Chronic diffuse nephritis (arteriosclerotic).

Red marrow of femur.

Chronic splenitis.

Loss of cerebral substance in right temporal region, and in lingula, with sclerosis of adjacent white matter and hippocampal gyrus.

General cerebral and cerebellar sclerosis.

Sclerosis of dentate nuclei (maximal) and of olives.

Sclerosis of lumbar cord.

Atrophy of cerebral cortex of frontal poles and of superior vermis of cerebellum.

Chronic leptomeningitis (vertical, superior cerebellar, and local about loss of substance in right hemisphere).

Bronchopneumonia with acute fibrinous pleuritis of both lower lobes.

Slight bruises of extremities.

Chronic periappendicitis.

Healed ulcers of stomach.

Chronic gastritis.

Chronic interstitial pancreatitis.

Chronic tympanitis.

Chronic adhesive pleuritis (right apex).

Following is a description of findings in the head:

Scalp normal. *Calvarium* dense, without diploe. *Dura* adherent to calvarium over vertex. *Dural sinuses* normal. Arachnoidal *villi* moderately thickened. *Pia mater* of vertex opaque and five or six times as thick as usual, so that the cerebral markings are quite effaced. The pial meshes are distended with clear liquid which stands out in sac-like accumulations over the atrophic frontal poles. The pial thickening is sharply marked off on the flanks of the brain, so that the temporal regions are spared on both sides. The pia mater of the temporal regions and of the base is a trifle more opaque and thicker than normal. The cerebellum and the substantia reticularis alba of Arnold show the greatest pial thickening found at the base. The pia mater covering porencephalic area in right posterior region is thick and cloudy. Large vessels with primary and secondary branches diffusely yellow and stiff with occasional short stretches of grossly normal tissue. *Brain weight* 1290 grams. Substance everywhere firm and elastic. Cerebellum notably firmer than cerebrum.

Cortex in superior vermis shows reduction in depth by one-half. Dentate nuclei of cerebellum cut with difficulty and have a leathery feel. Olives perhaps a trifle firmer than usual. Gray matter of frontal poles reduced one-half in depth and a trifle firmer than remainder of cerebrum. Extensive *loss of substance in right hemisphere* under floor of posterior cornua of lateral ventricle. Pia and ependyma here lie in apposition over a rounded oblong area 6.5 × 2 cm. in diameter, extending from the frontal plane posterior to the uncus to a frontal plane 2 cm. anterior to the occipital pole. The loss of substance involves the greater part of the cerebral tissue between the collateral, calcarine, and third temporal sulci. The white matter of the centrum semiovale anterior to this loss of substance is leathery. The hippocampal gyrus on the right is a third narrower and considerably firmer than that on the left. *Basal ganglia* a trifle firmer than usual. *Pons* firm, especially near periphery. *Cord* shows considerable increase of consistence especially of the posterior aspect in the lumbar region.

Middle ears: Free from exudate. Fibrous thickening of drum heads, particularly left.

Case IV.—H. P., female, born 1829, of good heredity, at 72 years had a "shock" with cyanosis, convulsions, unconsciousness for some hours, and subsequent speech disturbance and muscular weakness. The convulsions continued at irregular intervals, sometimes several in a day, as a rule several a week, sometimes with remissions for weeks. Loss of memory, hallucinations, excitement, supervened at 74. Generalized convulsions at infrequent intervals, especially at night, followed by confusion, paraphasia, complete disorientation, and incapacity to name objects. Death at 76.

The autopsy (three and one-half hours after death) showed the following conditions:

Hemorrhagic infarction of left ventricle of heart.

Aortic, coronary and iliac arteriosclerosis with calcification.

Renal and cerebral arteriosclerosis without calcification, but involving small as well as large branches.

Mitral sclerosis.

Chronic fibrous myocarditis.

Chronic fibrous endocarditis.

Hypertrophy and dilatation of left ventricle of heart.

Chronic interstitial nephritis.

Bronchopneumonia of hypostatic distribution.

Cholelithiasis.

Congestion of diplœ.

General cerebral atrophy (especially frontal and parietal).

Chronic fibrous leptomeningitis.

Compensatory edema of pia mater.

Small superficial area of yellow softening in left angular gyrus.

Following is a description of findings in the head:

Diplœ deep and congested. *Pia mater* and *sinuses* not notable. *Pia mater* over frontal and parietal regions hazy, thickened and distended by considerable fluid. Slight haziness over basal cisternæ. *Vessels* of circle of Willis and primary branches extensively sclerotic. Small cortical branches everywhere prominent. Marked sclerosis of pial *vessels* overlying small superficial area of yellow softening in region of left angular gyrus. The convolutions of the frontal and parietal regions are narrowed and in places present broad cupping of their surface together with shallow and wide sulci. The brain substance is of normal consistence. The ependyma of the ventricles is smooth.

I present in Plate XVI the cell appearances in the orbital region of a confirmed epileptic (Case V). The reduction in number of elements in the outer layers is striking (comparable to appearances in Plate XII and Plate XV). The atrophy is somewhat general, but, as in numerous instances, the smaller elements suffer first. This section is only an example of what may be found in numerous regions of this case. Palpable sclerosis was confirmed to a part of the right central and frontal regions.

The details follow:

Case V.*—A. H., negress, born 1860. Convulsions appeared in the patient's early thirties and were frequent for a month. They returned again at 39 years, but occurred at rather infrequent intervals. Remarkable ophthalmoptosis, giving rise to the suspicion of brain tumor. Vision fairly well preserved. Ophthalmoscopic examination showed only swollen veins. Headache. Increasing weakness. Slight external strabismus (left). Left knee-jerk slightly brisker than right. Impairment of memory. Emaciation. Conjunctivitis. Hypopyon. Death in coma at the age of 46. No convulsions were noted during the last two months. Irregular course movements of arms.

The autopsy (eleven hours after death) showed the following conditions:

Encephalomalacia and myelomalacia.

Early bronchopneumonia left lower lobe.

Sclerosis of middle two-thirds of right central convolutions and posterior part of right middle frontal convolution.

Atrophy of left optic nerve.

Conjunctivitis, keratitis and hypopyon of left eye.

Left ophthalmoptosis.

General arteriosclerosis (aortic, coronary).

Slight mitral sclerosis.

Old infarct of kidney.

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* Published more fully in a "Note on Cell-Findings in Soft Brains," by E. E. Southard and M. B. Hodskins, Am. Journ. Insanity, Vol. LXIV, p. 305.

Chronic external adhesive pachymeningitis.
Chronic adhesive pleuritis.
Chronic focal adhesive pericarditis.
Mural and subperitoneal fibromyomata of uterus.

Following is a description of findings in the head:

Scalp edematous anteriorly. *Calvarium* thick, with little diplœ. *Dura* adherent to calvarium in bregmatic region. *Sinuses* normal. *Pia mater* edematous, without notable thickenings. *Brain weight,* 1055 grams. Substance remarkably and evenly reduced in consistence in both white and gray matter. Olives and dentate nuclei as soft as normal cortex cerebri. The appearances resemble those of many days post-mortem. The central convolutions of the right hemisphere are much firmer than the surrounding convolutions. The right ascending frontal convolution is firm throughout the arm area and for a portion of the face and leg areas. The right ascending parietal convolution is equally firm for a like distance. The sclerosis is sharply marked off by sulci, by the post-central sulci behind (so as to exclude the superior parietal and supramarginal regions) and by the anterior ramus of the inferior precentral sulcus and the superior frontal sulcus in front and above (so as to exclude the greater part of the middle frontal and the superior frontal gyri). There is no demonstrable atrophy or chronic pial reaction in relation with the sclerosis. The white matter beneath presents no change except the universal reduction in consistence.

Cord: Numerous calcified plaques in posterior lumbar pia.

Middle Ears: Left middle ear contains semi-liquid pus.

Retinæ removed from behind show left nerve-head reduced, about one-third in surface area. *Vessels* injected.

Plate XVII exhibits the right precentral (leg) area in an epileptic of long standing (Case VI). *There is marked atrophy of the smaller elements with maintenance of the great motor cells intact.* As the autopsy report shows, there was extensive sclerosis in many parts of the nervous system. Yet the motor cells remain, forming parts of an extremely simplified series of arcs.

Case VI.—W. R., male, born in 1854, began to have convulsions at seven years of age, after whooping cough. The convulsions were severe, averaged one a month, and ceased to occur about 1884. About 1899 the convulsions reappeared and dementia became pronounced. The patient was admitted to hospital January 15, 1906. The left leg was found somewhat smaller than the right, whereas the arms were equal. The toes of the left foot were extended at the first joint and flexed at terminal joint. Instability in Romberg position. Left leg weaker than right. Vision of right eye diminished. Slight internal strabismus. Pupil reactions normal. Knee-jerks lively. Left knee-jerk and Achilles jerk more lively than right. Babinsky of left side. Stupid, untidy, grimacing, snarling and irritable. In February his mood changed to a laughing childish dementia. Convulsions appeared in April. Gradual failure. Death December 28, 1906.*

The autopsy (twenty-three hours after death) showed the following conditions:

Occlusion of larynx.

Congestion and edema of lungs.

Chronic diffuse nephritis.

Congestion of kidneys.

Congestion of mesenteric veins.

Calvarium dense.

Chronic external adhesive pachymeningitis.

Chronic fibrous leptomeningitis over left superior parietal and left central gyri, hippocampal gyri, and superior vermis of cerebellum.

Sclerosis of dentate nuclei.

Sclerosis of pons.

Sclerosis of hippocampal gyri, of orbital regions, of precentral gyri, of post-central gyri, of posterior part of superior parietal lobules, of fusiform lobules (slight).

Sclerosis about posterior horns of lateral ventricles.

Anomalous fissuration of superior vermis of cerebellum.

Following is a description of findings in the head:

Hair short, streaked with gray, thin on top. *Scalp* normal. *Calvarium* shows no diplœ. *Dura* adherent over occipital and superior parietal regions where, notably on the left side, there is a cluster of villi surrounded by moderately thickened pia mater. *Pia mater* thin and transparent everywhere except along lip of longitudinal fissure on left side in region of arachnoidal *villi* and over left central convolutions, along inner borders of both hippocampal gyri and over superior vermis of cerebellum especially in the region of the clivus monticuli. The posterior wall of the cerebellopontine cisternæ and the pia maters about the surrounding cisternæ in the region of the optic chiasm are moderately dense and suggest no notable degree of fibrosis. Vessels show nowhere any trace of sclerosis or lesion. The veins of the vertex are moderately injected but the small vessels over the surfaces of the gyri do not stand out prominently. *Brain weight,* 1290 grams. The brain substance shows striking varieties in consistence. The laminæ of the superior half of the cerebellum including the vermis show the best marked loss of consistence, anywhere shown; and this loss of consistence appears to be sharply limited posteriorly by the horizontal fissure. On section this loss of consistence proves to be superficial and the white matter of the arbor vitae is as firm as elsewhere. The dentate nuclei show an increase of consistence in both hemispheres. The posterior third of the pons is softer than the anterior two-thirds; the difference is probably due to gliosis of the anterior two-thirds. On section the pons appears to show some graving out in the central regions superior to the pyramidal tracts. The central gray matter is far softer than the rest of the pons. The *cerebral hemispheres* show palpable indurations, (1) of both hippocampal gyri, (2) of both orbital regions for a space 1 cm. in diameter surrounding the olfactory bulbs, (3) the upper two-thirds of both precentral gyri, best marked on the left side where the induration extends a trifle posteriorly to include the post-central convolution, (4) both post-central gyri in less degree than in precentral, (5) both superior parietal gyri in their posterior halves, (6) in slight degree both fusiform lobules. The maximal palpable induration is found in the superior part of the left precentral gyrus and in the two cornua ammonis where they project into the ventricles. The dentate nuclei of the cerebellum are almost as firm as the regions just noted. The *lateral verticles* contain little fluid and show no ependymitis. There is slight induration of white matter surrounding the tips of both cornua. The basal ganglia show no evidence of lesion. The two optic thalami appear of nearly equal size; the left globus pallidus is slightly yellower than right. The *cerebellum* measures 10.8 cm. in greatest lateral diameter, the superior vermis measures 5 cm. to the cerebellar notch. The cerebellar notch appears a little deeper than usual on account of encroachment of fossa which hollows out the posterior half of the superior vermis, halving especially the clivus monticuli. This fossa is smooth walled and overlaid by a moderately thick layer of fibrous tissue. The fissural markings of the left lobus clivi do not run concentrically about into their fellows of the right lobus clivi. The left lobus clivi is divided into three sets of folia separated by deep fissures. The superior set of folia clivi dips sharply upward in the hollow of the anomalous fossa of the clivus monticuli so as to become continuous with the middle set of folia in the right lobus clivi. The appearance is thus presented of sharp termination of the superior set of folia in the right lobus clivi internal. Sagittal sections show a corresponding disturbance of the fissuration. A section slightly to the left of the median line shows that the folia usually exhibited in the clivus monticuli are replaced in a small area not over 1 cm. in diameter by the flat nonfoliated tissue. Adjacent sections rapidly regain the normal fissure appearance. This lesion may be interpreted as a loss of substance of long standing. The overlying fibrosis may perhaps be interpreted as a reaction to the original injury. *Spinal cord:* Fairly firm. Cervical region softer than usual. Lumbar portion firmer than usual. *Middle ear:* Normal. Pituitary body congested.

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* I am obliged to Dr. H. W. Mitchell for these notes, drawn from the records of his Danvers service.

Plate XVIII is also derived from Case VI, but may be considered together with Plate XIX from Case III, as showing similar phenomena. Attention is here directed to remarkable gaps of an atrophic character in the closely set cells of the stratum granulosum of the cornu ammonis. The lesion in Case VI was nowhere found related with vessels. The focus shown in Plate XIX (Case III), like foci in other sections from the case, seems related to the presence of a vessel. These atrophic foci are, as adjacent sections stained by the Benda method demonstrate, attended by considerable gliosis.

Such changes are by no means confined to the cornu ammonis in cases of epilepsy, but in the close search of his cases made by a worker in epilepsy such changes are not rarely found. The archipallium is thus the scene of certain lesions of the receptive apparatus whose meaning we cannot yet make out. In the archipallium, although we have to do with similar (in the sense of less coordinated, less inhibitory) mechanisms, we also have to do with more compact structures in which small lesions may bring about relatively more irritation than lesions of the same volume set anywhere in the higher apparatus. This may serve as a suggestion why cornu ammonis lesions are relatively so apt to the production of powerful irritations. In Case I we dealt with an effective epileptogenic focus of small diameter; but it is possible that other cases might yield still smaller foci, were methods of examination fine enough.

In the above selection of cases I have brought out certain points with undue clearness with the object of supporting certain contentions of a general character. Whether or not the detail of these inductions is in all ways accurate, I hope that it is plain that the classical fiber-tract studies will not solve the problem. I have, however, steered clear of making any inductions from neurofibril preparations, because, as is well known, positive pictures of neurofibrils have far more convincing power than negative pictures. The problem, I believe, rather resembles that of multiple disseminated sclerosis than any other with which I am acquainted. The natural history of gliosis, were it completed, would go far to settle many problems, but particularly these.

I have, therefore, employed for the nerve cells the best general method for their demonstration that I know—the original method of Nissl (with very few and quite inessential modifications)—and have obtained an adequate picture of the neuroglia *in adjacent sections* by the Benda method for neuroglia (after alcohol fixation). In this way it is possible to attain a better conception of mechanical conditions surrounding cell-groups than by any other methods known to me. Moreover, these methods are quite simple and repeatable. The Nissl method is not precarious or capricious. The Benda method, though perhaps inferior to the Weigert and the Mallory methods under the best conditions, is wholly adequate for pathological neuroglia in most cases, and has the tremendous advantage of being *applicable to sections adjacent to the Nissl sections.* Nevertheless, I believe the important points of the present paper could probably all be made with far simpler methods, with any method which stains cells well and preserves the stratigraphy of the cerebral cortex.

SUMMARY.

The theory of epilepsy expounded in the present paper is founded mainly upon structural considerations. The histological data have been interpreted largely from a functional point of view. The theory lays claim to some originality in two directions, in setting forth, namely, the properties of a typical epileptogenic focus in the cerebral cortex, and the nature of that change in cortical tissue which favors epileptic discharges. The characteristic feature of a typical prime focus is described as the separation of a normal cell-group from its normal control by other cell-groups and the impact upon the receptive surfaces of these normal cells of a steady, intimate, abnormal pressure—both segregation and compression effected by neuroglia overgrowth. That feature of cortical tissue which favors the spread of epileptic discharges is described as due to a simplification of cell arrangements, arising in the destruction of controlling elements with maintenance of motor elements. In the production of both prime focus and the abnormal tissue which permits uncontrolled discharge, the neuroglia tissue plays a characteristic part—exerting an active continued pressure in the first instance, and readily permitting lateral discharges and the activation of great groups of motor cells in the second instance. In the former case we see a fresh example of the irritative property of heightened tension—only here exhibited quite in miniature. In the latter instance we are dealing with conditions of still greater theoretical interest, approximating, though with diverse outcome, the loss of insulation seen in foci of disseminated sclerosis. The findings suggest the widely different effects upon nervous tissues of active and of quiescent gliosis.

From a review of pertinent literature, it appears that physiological interest is converging upon the field here considered. Fiber-tract studies have failed to cope with other problems than those of linear transmission along well-insulated paths. Only in the case of multiple disseminated sclerosis and certain studies in interstitial neuritis, have the occurrence and nature of lateral discharge from fiber to fiber and the effects of intimate fiber pressure been considered. And in these instances it may well be proposed that a fresh abnormal type of synaptic tissue has been provided. Physiological interest is now levelled upon the synaptic tissues in general. And, if a synapse is a physical surface of separation between neurones, it is serviceable to inquire what are the conditions which can readily modify the synapse. The neuroglia tissue, formerly regarded as purely supportive in function, here rises to a high scale of importance. The present essay points out two effects of gliosis upon synaptic tissues, the one an active irritative one, the other a passive effect. A review of the fundamental views of Hughlings Jackson serves to demonstrate the perfect generality of epileptic phenomena at all levels, and makes clear why the writer sought knowledge about epilepsy in organic cases. If the writer advances a case in which the prime epileptogenic focus consists in an active gliosis within a space of one cubic centimeter in the cornu ammonis, he cannot be charged with holding that all cases of epilepsy are so brought about. He describes what he regards as a typical prime focus. He conceives fundamentally that similarly forcible and lasting stimulation of a receptive surface, standing in important relations to the motor system, might produce epileptic convulsions just as effectively as the gliosis he describes. In this sense complex emotions or intestinal worms might conceivably stand in as effective a relation to the nervous system as the intimate pressure of early gliosis upon the expansions of elements whose currents eventually play upon the muscular system.

Wholly distinct from these considerations about epileptogenic foci are those points which are developed concerning tissues facilitating discharge. A review of various authors discovered much difference of opinion and considerable interpretation of phenomena as secondary. The phenomenon of gliosis has not escaped numerous observers, among them the very observers that have emphasized the alterations of the second cortical layer as important in epilepsy. But this gliosis has been regarded as secondary, and our attention has been diverted rather to certain cell and nuclear characters which are looked upon as specific. The writer has been tempted to regard these nerve-cell changes as vegetative and at any rate as not further analyzable, but to accept them as examples of a lesion which will interfere with normal control of muscular elements. The cases presented here go far to prove that the nerve cells of the outer layers are the first to disappear in cases of atrophy and even along the edges of ischemic areas. The tendency to the formation of tissue favorable to epileptic discharge is, according to this view, a somewhat general tendency in cerebral tissue, so long as the destroying forces stop short of the motor elements and permit any communication, however slight, between the motor elements and the receptive side of the body. A reduction or simplification of the system through destruction of the smaller elements of the cerebral cortex procures new reflex arcs with fresh surfaces of separation which are perhaps even simpler and more automatic than the spinal arcs and synapses. The peculiar features of the epileptic discharge depend upon the inertia of currents travelling in simplified arcs, and upon the lack of energy-absorbents en route. The cerebral arcs normally escape automatism through a multitude of synaptic connections; under epileptic conditions the cerebral mechanism approaches in fatality the spinal mechanism. Under this conception epilepsy and phenomena like clonus are readily perceived to belong to a single logical group.

The phenomenon of epilepsy, in short, requires the intactness and even the normality of some well-defined route from stimulus to muscles. If we conceive the stadia of this route set end to end with the cerebral synaptic tissue in the middle, we perceive that toward the two ends of the linear series it becomes increasingly difficult to provide conditions which will produce generalized and spreading convulsions. Destruction of elements at any point in the route should at first sight exclude the production of epilepsy. And so, in most cases, the destruction of the efferent paths will exclude epilepsy. In the afferent paths, however, the very process of destruction often constructs new and potent surfaces of stimulation which act as epileptogenic foci; and, in the cerebral synaptic tissue, the strata are so constructed that the loss of smaller, central, modifying, and inhibitory elements is effected prior to the loss of the major elements which are essential to the intactness of the great route. And these major efferent elements can themselves be subject from time to time to stimulation afforded by the contractile energies of growing neuroglia. Epileptogenic stimuli are applied in all cases to those elements having a forward direction, so that the reaction is in most cases, if not necessarily a sensorimotor reaction in Hughlings Jackson's sense.

What are the applications of this theory to the phenomena of idiopathic epilepsy? In certain cases of idiopathic epilepsy there seems to be grave doubt whether any adequate epileptogenic foci can be discovered. There is more hope that *tissues favorable to epileptic discharge* shall be discovered, if the proper methods are employed.

We can see some reason for the absence of effective foci in hereditary cases, particularly if we bear in mind the epileptic offspring of Brown-Séquard's injured guinea-pigs. With the onset of topographic and stratigraphic knowledge of the cerebral cortex, we shall approach more nearly to a definition of tissues suitable for the propagation of epileptic discharges. So far it seems that such synaptic tissues are characterized by abnormally simplified arcs whose impulses are the more automatic through the lack of countercurrents from surrounding cells. Whether we are to look in inherited serum properties for the production of such conditions, the future will decide. Destroying agents of moderate power tend to alter tissues in this direction.

REFERENCES.

1. Foster and Sherrington: Text-book of Physiology, III, London.
2. Sherrington: The Integrative Action of the Nervous System, 1906.
3. Anderson: Epilepsies and Insanities. Hack Tuke's Dictionary of Psychological Medicine, 1892, Vol. I, pp. 440-450.
4. Ohlmacher: Bulletin of Ohio Hospital for Epileptics, 1898.
5. Voisin et Péron: Arch. de Neurol., 1892, T. XXIV, p. 178.
6. Krainsky: Zur Pathologie der Epilepsie. Allg. Zeitschr. f. Psych., 1898, LIV, p. 612.
7. Ceni: Medical News, March 8 and 15, 1902.
8. Bra: Du parasite trouvé dans le sang des epileptiques. Revue Neurol., 1902.

9. Mott: Archives of Neurology, I, p. 493.
10. Gowers: Epilepsy and Other Chronic Convulsive Disorders, London, 1881.
11. Oebeke: Berliner Klin. Wochenschr., 1880.
12. Hughlings Jackson: On a Case of Fits Resembling Those Artificially Produced in Guinea-pigs. Med. Soc. Proc., London, 1887.
13. Brown-Séquard: Summarized in Richet's Dictionnaire de Physiologie, Article Cobaye, III, p. 926.
14. Nothnagel: Ziemssen's Cyclopaedia, XIV.
15. Schröder van der Kolk: New Sydenham Soc. Trans., 1859, London.
16. Adolf Meyer: Medical News, New York, 1903.
17. Bevan Lewis: Text-book of Mental Diseases, London, 1889.
18. Clark and Prout: American Journal of Insanity, 1900, 1903-4.
19. Mott: Croonian Lectures, 1900.
20. Campbell: Histological Studies on the Localization of Cerebral Function, 1905.
21. Prus: Ueber die Leitungsbahnen und Pathogenese er Rindenepilepsie. Wiener Klin. Wochenschr., 1898, No. 38.
22. Prus: See also Lewandowsky. Die Funktionen des Zentralen Nervensystems, 1907, Kap. XIV.
23. Kussmaul und Tenner: Ursprung und Wesen der fallsuchtartigen Zuckungen. Frankfurt, 1857.
24. W. A. Turner: Epilepsy: A Study of the Idiopathic Disease, 1907. Chapter VIII contributed by John Turner.
25. Bevan Lewis: Text-book of Mental Diseases, 1890.
26. Clark and Prout: Status Epilepticus: A Clinical and Pathological Study in Epilepsy. Am. Journ. Insanity, October, 1903.

PLATES.

All the photographs, except Plate X, have a magnification 1 : 45, Plate X, 1 : 40. All the sections, except those photographed for Plate X, were prepared and stained according to the method of Nissl (without essential modification). The sections photographed for Plate X were prepared from blocks fixed in Zenker's fluid and were stained according to Mallory's phosphotungstic acid hematein method for neuroglia. I am indebted to Mr. L. S. Brown of the Massachusetts General Hospital for most of the accompanying photographs.

PLATE X.

Focal Scleroses in (A) Plexiform Layer; (B) Perivascular Region from Precentral Cortex in a Case of Organic Epilepsy Arising in Old Age. Such scleroses, though frequent in certain cases of epilepsy, are not regarded as bearing in an important way upon the problem of epileptic discharges.

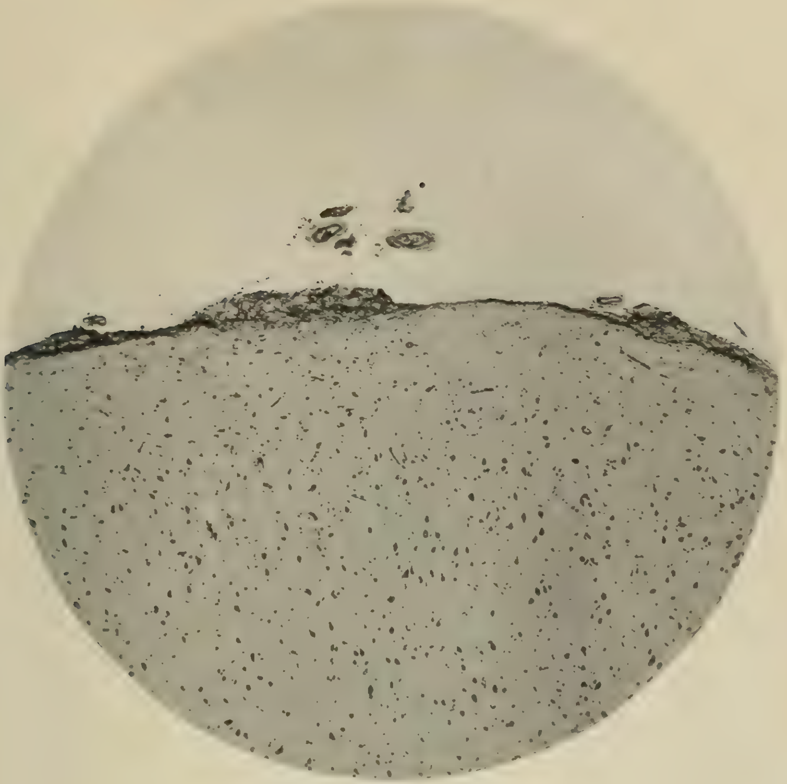


FIG. 1.

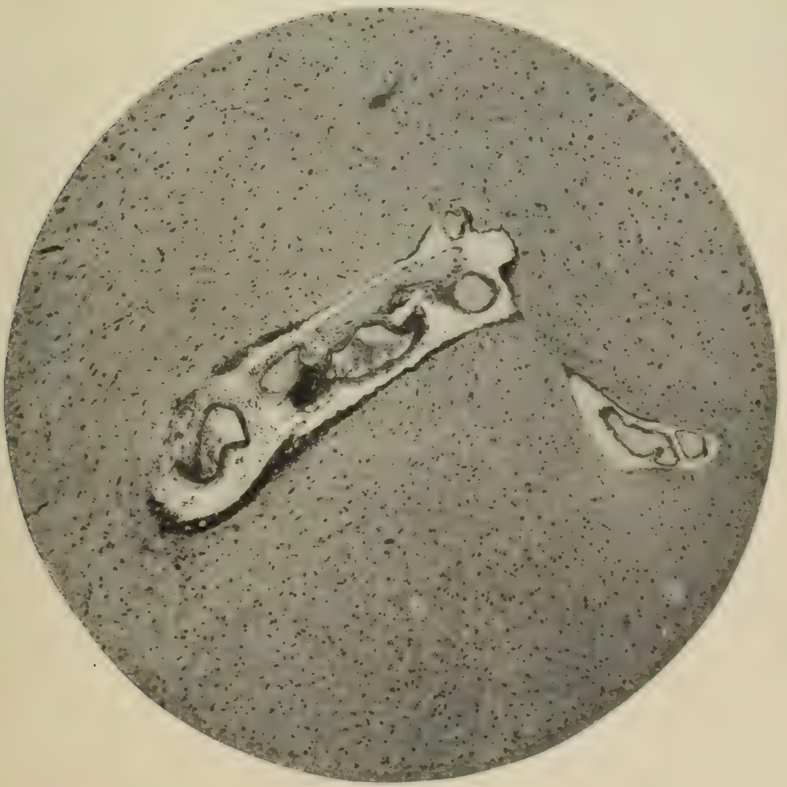


FIG. 2.

PLATE XI.

Acute Encephalitis Focal in One Cornu Ammonis in a Case of Epilepsy Lasting Nine Weeks and Terminating in Status. The great nerve cells are still intact, but between the nerve cells are great numbers of proliferating neuroglia cells, amounting externally to a dense black zone. As a bit of intact nervous apparatus under abnormal pressure conditions, the cells of this area—nowhere greater than 1 cm. in diameter—are capable of acting as an Epileptogenic Focus. A severer lesion might destroy the focus either directly or by cutting off the transmission of impulses toward the motor apparatus.

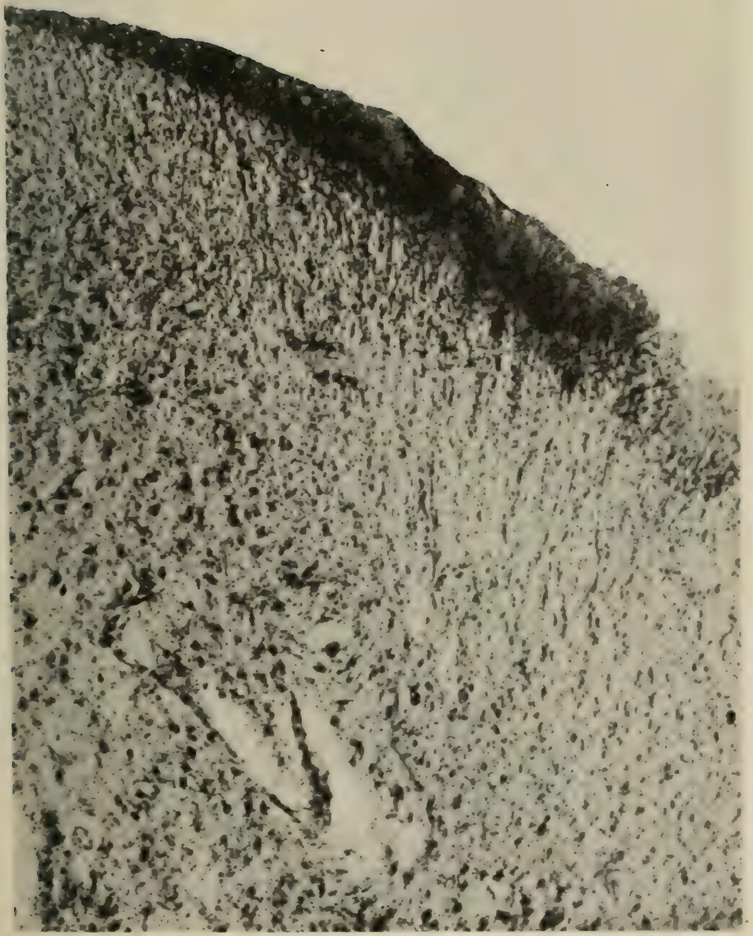


PLATE XII.

Differential Atrophic Process Involving Superior Temporal Gyrus in a Case of Aneurysm of Anterior Choroid Artery, Probably of Sixteen Years' Duration. Other gyri in both hemispheres showed evidence of similar differential atrophy. The Second Cortical Layer is cut by a lane of sclerosis at the left hand. But two appreciable islets of large cells remain in the Layer of Large External Pyramids. *The inner layers are fairly well preserved.* Compare particularly Plates XVI and XVII for similar reductions of a differential character in other gyri and other cases. Compare Plates XIII and XIV for theoretically similar reductions in cases of multiple miliary infarctions of the cortex.

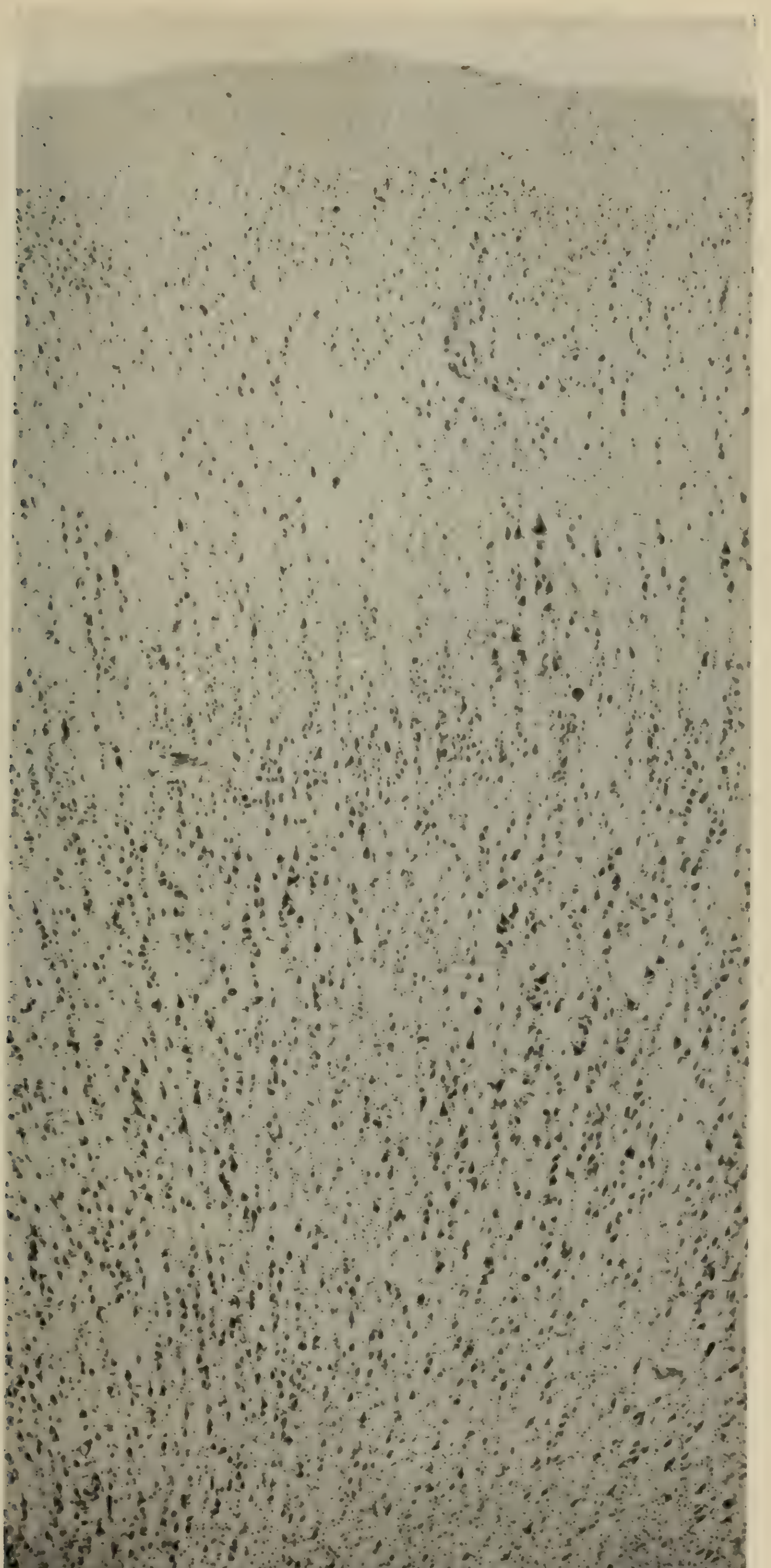


PLATE XIII.

SMALL OLD INFARCT OF PRECENTRAL CORTEX (trunk area) IN CASE OF ORGANIC EPILEPSY. Characteristic differential destruction of layers in which the SECOND AND THIRD CORTICAL LAYERS SUFFER MAXIMALLY. The larger cells appear more resistant. (Compare particularly Plate XVII for a theoretically analogous loss of smaller elements with maintenance of great motor cells of the leg area in a case of generalized atrophy.) The denuded area is filled with neuroglia tissue, containing relatively few nuclei and no longer exerting active pressure upon nervous elements. Synaptic tissue such as here shown possesses fewer modifying or inhibitory small elements than normal and is a tissue appropriate for epileptic discharges just in so far as the preserved elements have a "forward direction" of impulse (musclewards).

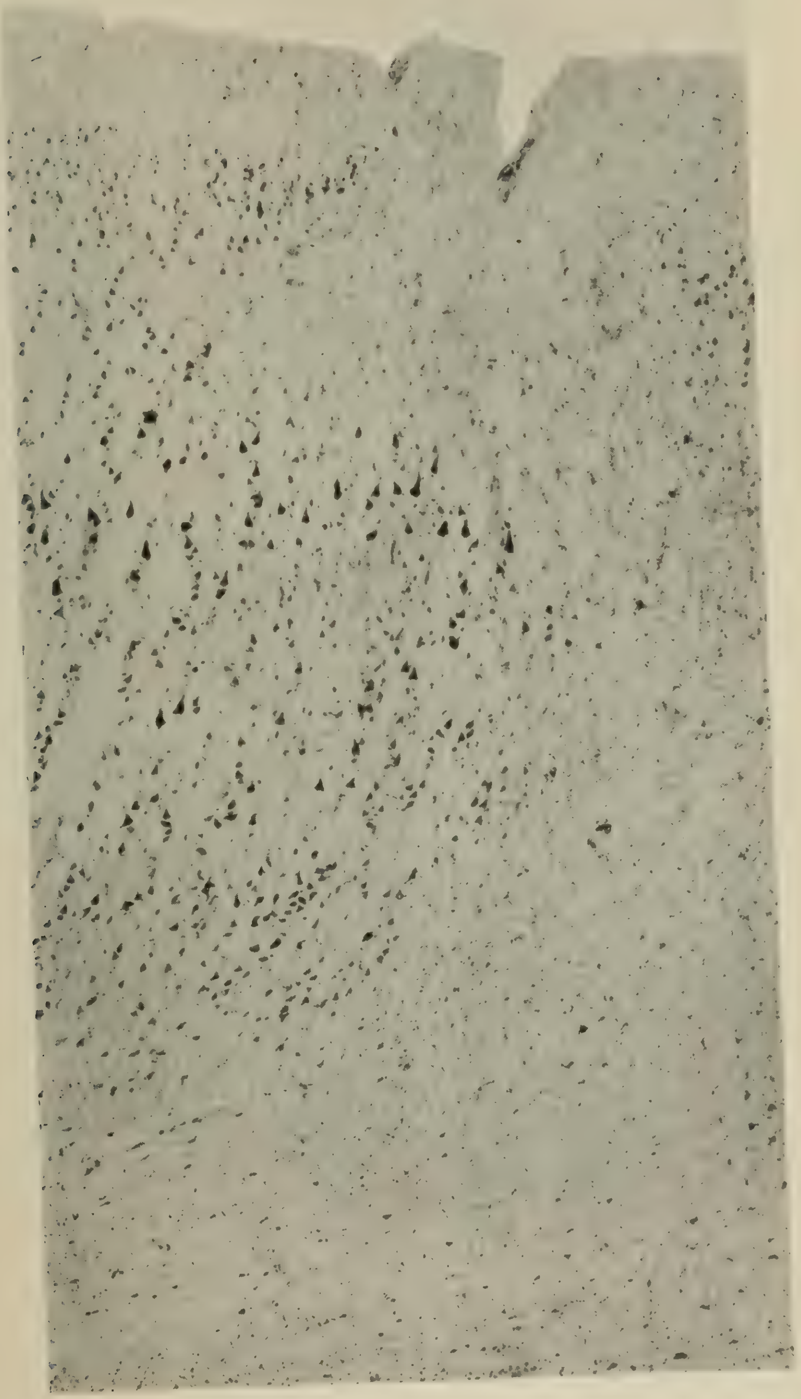


PLATE XIV.

(Same case as shown in Plate XIII.)

Early Infarct of occipital cortex with denuded area filled with neuroglia cell nuclei. The preservation of many large cells at the borders of the infarct is noteworthy (compare Plate XIII). The infarct is still capable of exerting active pressure upon the neighboring nerve cells, and this pressure is theoretically capable of serving as epileptogenic agent after the manner of the lesion shown in Plate X. The neuronic links having "forward direction" toward the motor region must, however, remain intact. The combination of such active (pressure-exerting) foci of sclerosis with older foci (like that in Plate XIII), which have destroyed much of the inhibitory apparatus, must favor epilepsy.

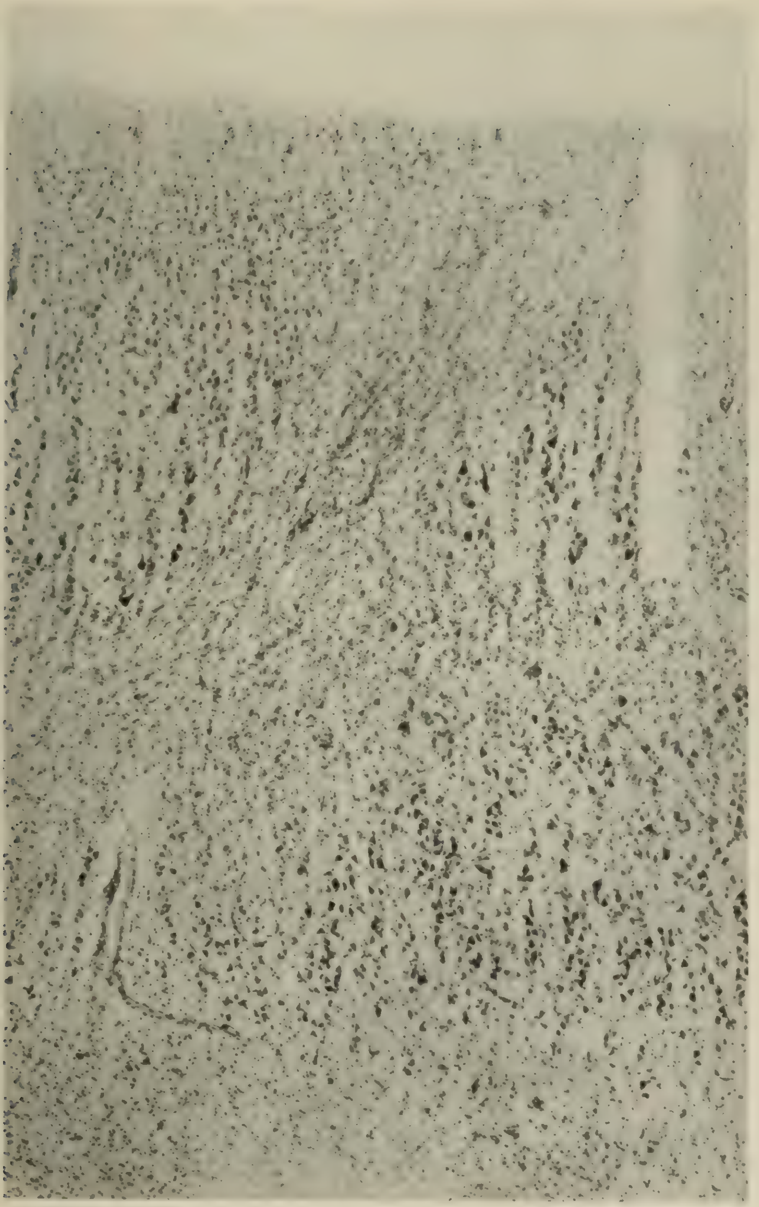


PLATE XV.

A SECOND CASE OF EPILEPSY SHOWING MULTIPLE SMALL INFARCTIONS, illustrating similar considerations to those of Plates XII and XIII.

1. Atrophy more marked in outer layers.

2. Maintenance of larger cell within borders of a small oval infarct.

The Benda preparation of an adjacent section showed this *normal cell imbedded* in *fibullar neuroglia*. Here is offered the theoretical possibility of impulses of an epileptogenic character set up directly in efferent elements. The more frequent finding of epileptogenic foci in "sensory" or receptive parts of the central mechanism is perhaps due to the greater extent of these mechanisms.

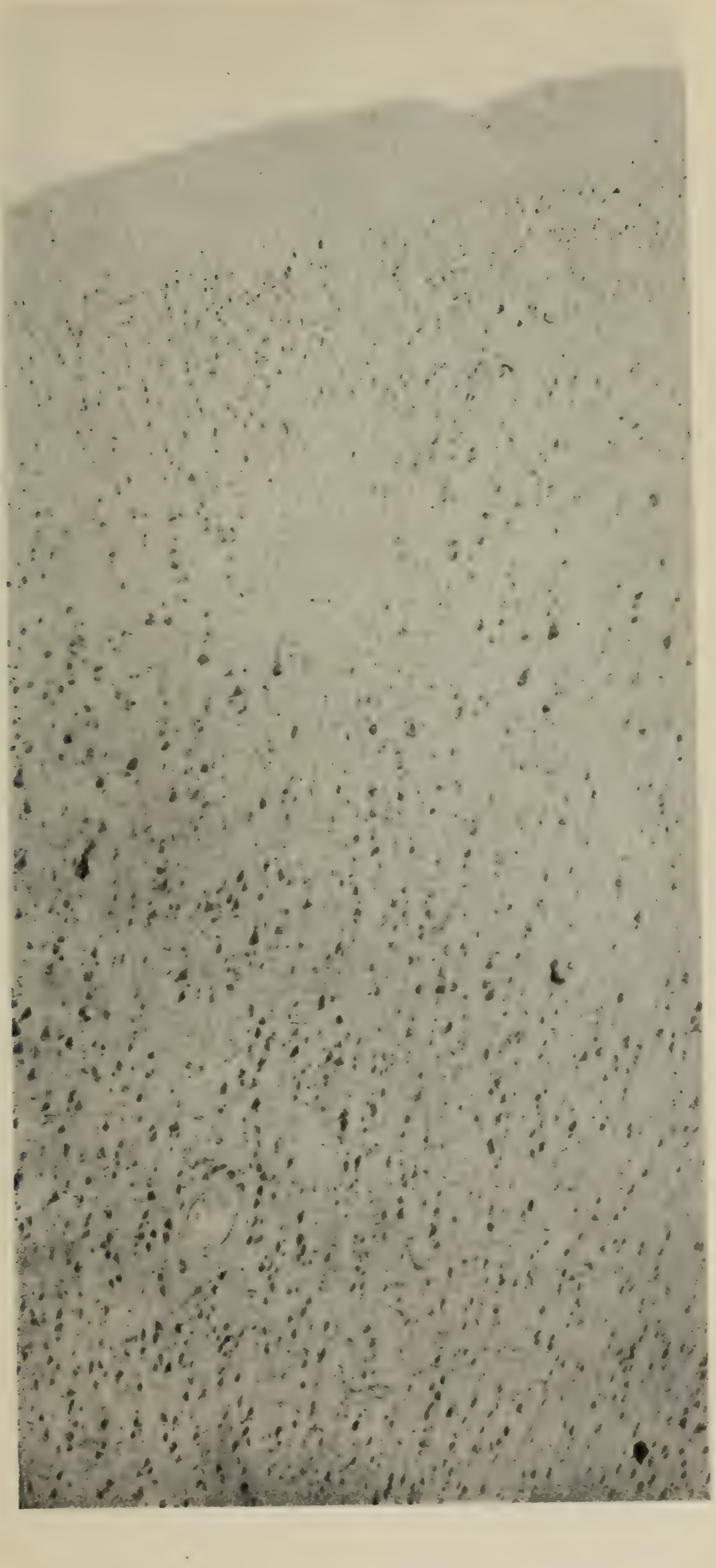
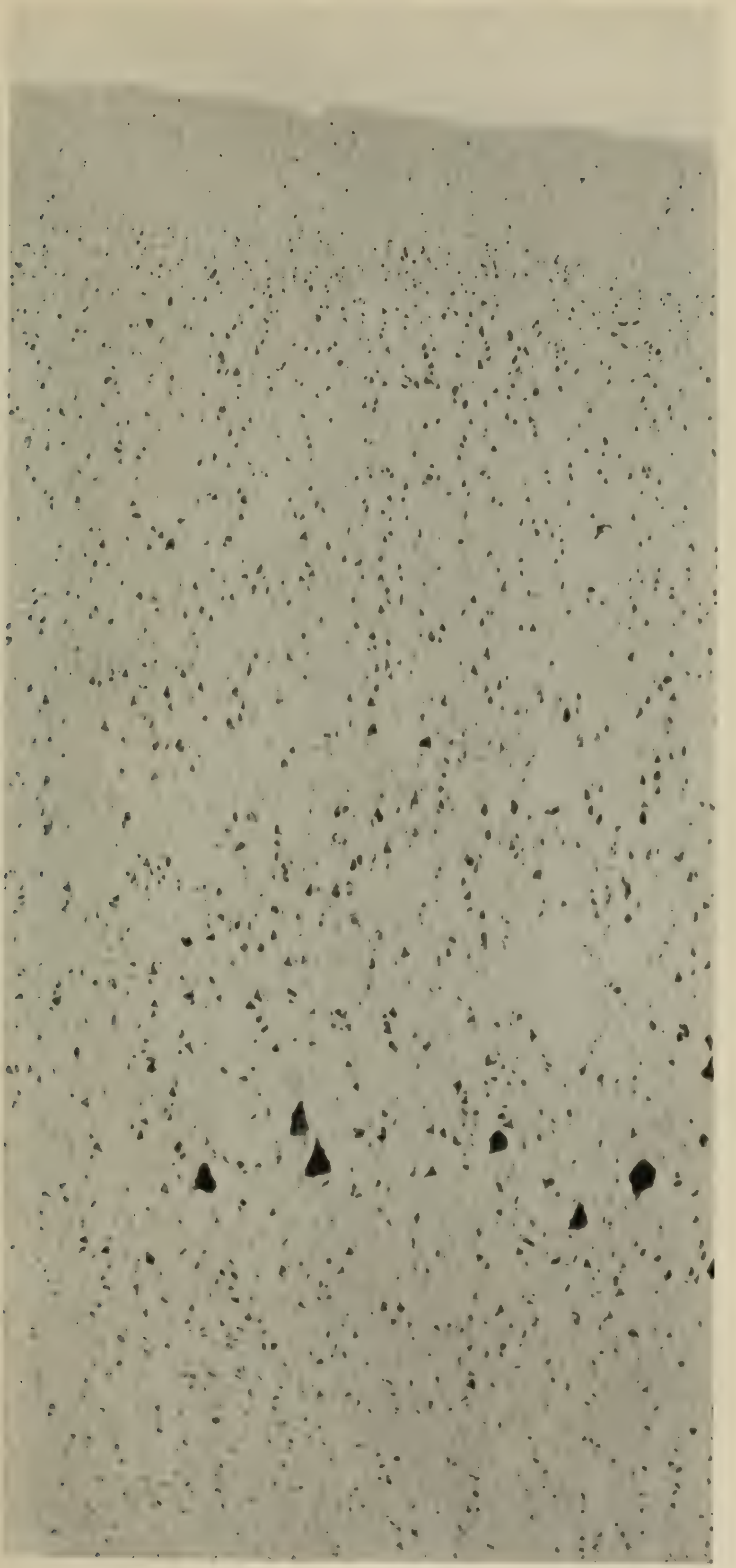


PLATE XVI.

ORBITAL CORTEX IN A CONFIRMED EPILEPTIC WITH MENTAL SYMPTOMS (epilepsy over ten years in duration). This area in common with numerous other cortical types showed a diffuse atrophy affecting most markedly the outer cell layers. (Compare Plates XII, XV, XVII.)

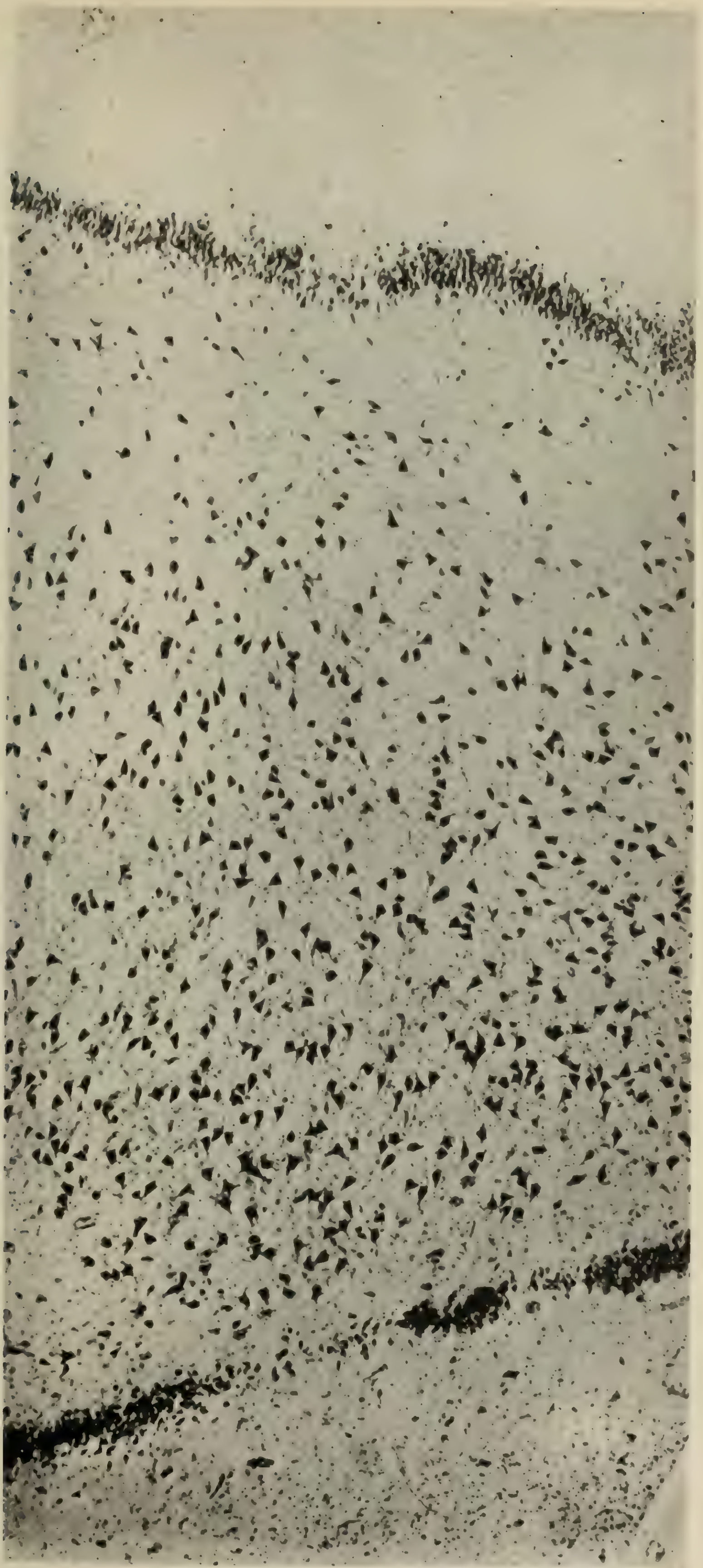
PLATE XVII.

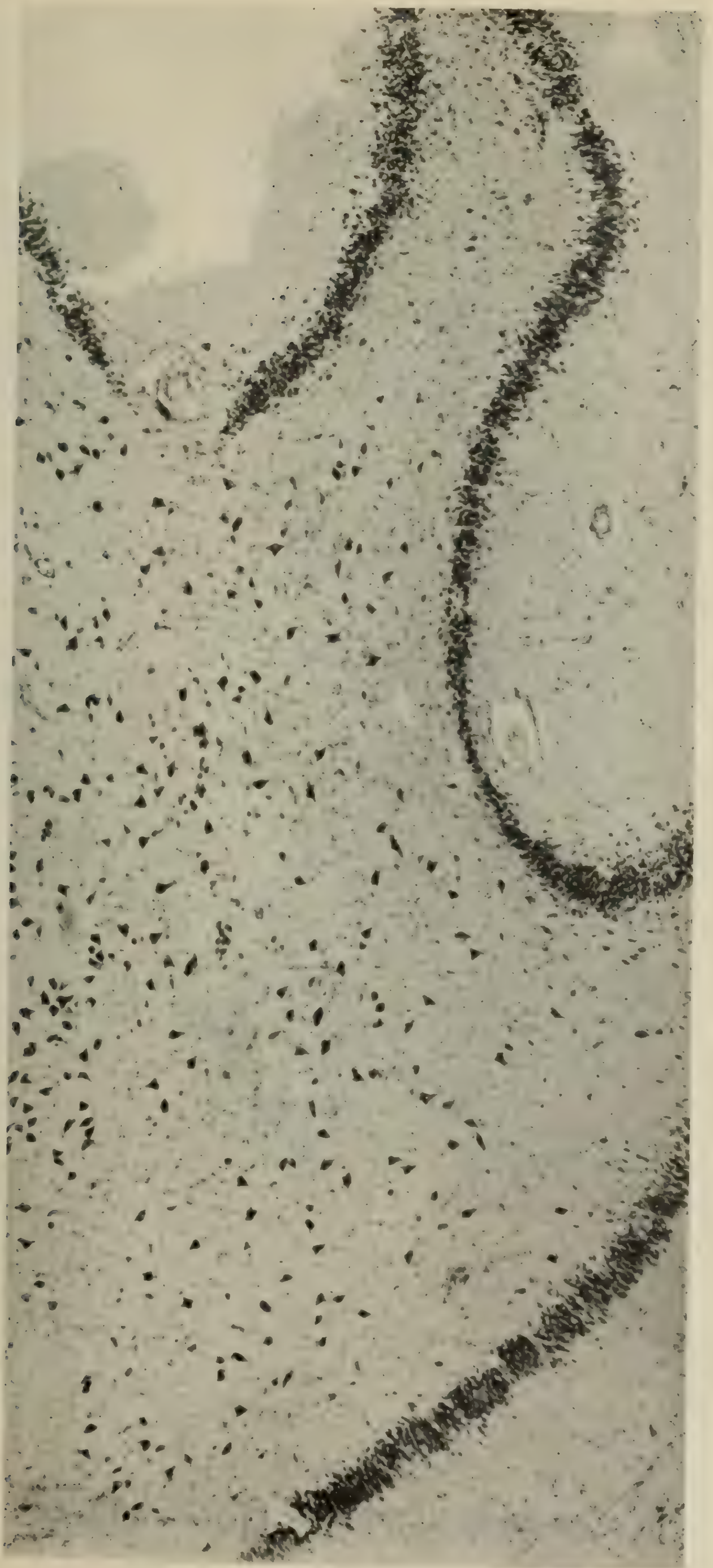
Diffuse Atrophy of Precentral Cortex. Notable Preservation of Larger Elements. Simplified or Reduced Synaptic Tissue Suitable for Automatic Discharges if Stimuli are Provided.



PLATES XVIII AND XIX.

Cornu Ammonis in Two Cases of Epilepsy. Minor Atrophic Lesions Interrupting Granular Strata. In Plate XIX one of the gaps is probably related to a vessel about which the Benda preparation shows an inactive gliosis. Such lesions frequently occur in epilepsy, but are sometimes found in non-epileptic cases. Early in their formation these lesions may possibly serve as epileptogenic foci, but this cannot be proved. The same conditions which produce them are found elsewhere in the cerebral cortex producing the milder differential lesions which render the tissue suitable for epileptic discharges. Plate XVIII comes from the same case as Plate XVII; Plate XIX from the same case as Plates XIII and XIV.





A COMPLICATED CASE OF BRAIN TUMOR.

By CHARLES RICKSHER, M. D.,
Assistant Physician, Danvers Insane Hospital;

WITH AN AUTOPSY REPORT

By E. E. SOUTHARD, M. D.,
Assistant Professor of Neuropathology, Harvard Medical School, and Pathologist, Danvers Insane Hospital.

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The following case is interesting both from the clinical and pathological sides by reason of the varied lesions and post-mortem findings:

The patient, L. W., was a married woman of 45 years and was admitted to the Danvers Insane Hospital on December 12, 1907. The history obtained from the husband is as follows:

Family history unknown. The patient was born in New Hampshire, and, as far as is known, the early life was uneventful. She first married at about twenty years of age and had one child, a boy, who is living and is healthy. She married her present husband 16 years ago. There were no children by this union.

The husband describes her as a mild, even-tempered woman who took things as they came and did not worry over trifles. She attended to her duties as a house-wife in an exemplary manner up to the beginning of the present illness.

The menstrual periods became irregular about four years ago and she passed the menopause about two and one-half years ago. At this time she was nervous and anxious, restless and agitated. After the menses stopped she recovered and regained completely her former disposition.

About twelve years ago she had some womb trouble accompanied with vaginal discharge and pain in the lower abdominal region. This disturbance lasted about three months during which she was unable to do any work but she was not confined to bed. About five years ago she had a left otitis media which yielded to treatment. About two and one-half years ago she again had a discharge from the left ear which lasted several weeks. The discharge occurred for the third time in August, 1907 but lasted only a short time. The husband denies any venereal trouble.

The present illness began in December, 1906. At this time the patient was very nervous, had headaches, and felt anxious concerning herself. The headaches are described as a feeling of a dull heavy pressure and seemed to extend from the forehead to the base of the brain and from which she seemed to gain relief by sleep. Change of position had no effect. She often spoke to her husband of becoming insane and wondered if she would have to go to a hospital. She was irritable and easily fatigued and when she exerted herself became very tired, out of breath and more irritable. She remained in this condition for three or four months and then the husband noticed he had some difficulty in understanding what she said. Her speech became quite indistinct and it would be necessary for her to repeat several times what she wished to say before her husband could understand her. She spoke as if she were tongue-tied. About this time the left side of the body became weak, especially the leg, although the weakness was also apparent in the arm. At times she would seem to give way on the left side. There was also some pain at the base of the brain. About June 1, on the advice of a physician, she moved to the country. After this there was an entire change. She became stupid and drowsy and slept most of the time. She became forgetful and could not remember little things about the house. She would ask her husband about her son sometimes twenty times in an evening without comprehending that she had asked him before. She did nothing on her own initiative but would undertake house-work if told to do it. The quality of the work was below her normal. She was dizzy and fell several times. Since August, 1907, she has taken no interest in anything. She would sit and gaze at space for hours. This continued until November, 1907, when she became quite restless and would sleep only under the influence of a hypnotic. She was untidy in her habits and would wet and soil herself.

About three weeks before admission she began to experience visual hallucinations, she saw pink rats and other animals running about the floor, baby carriages, and, according to her husband, about everything imaginable. For the two weeks preceding admission she had been unable to move about by herself and fell many times. She was very restless and would not stay in any place very long. The day before admission she failed to recognize her husband and asked who he was. At no time was there any nausea, vomiting or convulsive attacks.

On admission physical examination showed a well nourished woman. There was a marked ptosis of the left eyelid. The pupils were contracted, the left being larger than the right, both were central and slightly irregular in outline. It was extremely difficult to determine the light reflexes, but both pupils seemed to contract slightly to direct light and accommodation. There was a marked pyorrhoea. It was impossible to get the patient to protrude her tongue beyond her teeth. The heart sounds were clear and the radial arteries were not palpable.

The left leg was slightly atrophied and the patient was unable to move it. The left arm was somewhat smaller than the right and the patient was unable to flex the forearm on the arm. Muscle strength was less in the left arm than in the right. The left side of the face showed some paresis and the patient was unable to draw her mouth to the left.

The tendon reflexes were slight in the right arm and absent in the left. The knee jerks and patellar reflexes were active on the left side, they were slightly diminished on the right. Babinski's phenomenon was present on the left side, and not on the right. Schaefer's reflex, pressing the tendo Achilles between the thumb and index finger, caused a dorsal flexion of the great toe on the left side, a plantar flexion on the right.

As far as could be determined she could distinguish the head and point of a pin on both upper and lower extremities, on both sides. She was unable to use the left arm, there was no incoordination noticed in the right arm. Stereognosis for coins was good in both hands, the patient answering quickly and correctly. Several attempts were made to examine the eye grounds but the patient became nauseated and vomited at each attempt.

At no time during her stay in the hospital was there any evidence of hallucinations or illusions. Consciousness seemed to be clouded, the patient was quite apathetic and paid no attention to anything going on about her. Past events of a striking character were retained but there were many lapses. She gave the date as Friday, December 20, 1886, was unable to tell where she was and said she had been here one month. She was unable to answer correctly simple geographical and historical questions. She was able to perform simple problems in addition, but none in division.

The speech defect was quite noticeable. Only by close attention could one distinguish what she said and when asked a question she would repeat it several times before answering. The speech defect seemed to have two components, a stammering due to motor disturbance and an omission of words due to her mental condition. The handwriting showed a marked coarse tremor.

There was some insight, the patient saying that the paralysis followed a shock but she could not realize that the memory was disturbed. There was a tendency to laugh or cry on very slight stimulus.

She remained in bed during her stay in the hospital and gradually became more drowsy and less restless. At times she would weep and attempt to talk but the speech defect increased to such an extent that she could not be understood. About noon on January 22, while her husband was visiting her, she began to have some difficulty in breathing and became somewhat cyanotic. The right eye was turned upwards and inwards and showed a marked nystagmus which did not affect the left eye. The respiration became more difficult and she died at 2.45 p. m.

Autopsy Findings.

The autopsy was performed seven hours after death by Drs. E. T. T. Richards and M. M. Canavan. Following is a summary of such findings as are of interest in the present connection. It is planned to present a fuller account from the histopathological side at a subsequent time.

The cause of death is in doubt. The left middle ear contained 1-2 cc. of greenish pus from which a bacillus of the colon group was recovered in pure culture. The bacillus was not fatal to guinea pigs on intraperitoneal inoculation. The pericardium showed a slight acute fibrinous exudation of recent date. The relation between the otitis media and the pericarditis is in doubt. Culture from the heart's blood was negative, as also from the cerebro-spinal fluid. There was a mild acute degenerative nephritis superimposed upon a chronic interstitial nephritis.

The findings in the nervous system are probably more significant than those of the trunk. Both Gasserian ganglia showed somewhat recent chronic exudative processes of similar character, with giant cell formation and accumulation of lymphoid and plasma cells but without caseation or vascular lesions. Neither tubercle bacilli nor, by the Levaditi method after formalin fixation of one of the ganglia, spirochætæ, were demonstrable in these lesions of the ganglia.

The source and character of the Gasserian lesions are difficult problems. Possibly the left middle ear was the source of an infection with which these lesions are connected. Further work is in progress to find what relation the bacillus of the colon group, isolated from the ear, may have to the lesions. It is probable that the most reasonable hypothesis concerning the lesions is that they are tuberculous, despite the absence of bacilli in the sections. It is probable that the left-sided ptosis may be due to involvement of the third nerve in the chronic exudation, which can be demonstrated to be advancing beyond the capsule of the Gasserian ganglia.

The findings in the central nervous system were manifold:

(1) A dural endothelioma of the left side—the hemiplegic side in this subject—measuring 4 x 3 x 2.5 cm. deep, occupying a position between the superior frontal, anterior ramus of inferior precentral, paramesial frontal, and middle frontal sulci (Quain's nomenclature). Study of the underlying cerebral cortex fails to demonstrate more than a mild gliosis, as a result, doubtless, of the very slow and gradual tissue absorption running *pari passu* with the tumor's development. It was supposed that the tumor might, in some way, be responsible for the homolateral hemiplegia, but further study disposed of this possibility.

(2) Arterio-sclerotic lesions. The basal arteries were smaller than normal and showed areas of sclerosis at points of branching. There was no gross demonstration of arteriosclerosis in the smaller vessels. On section of the pons multiple small cysts of softening containing numerous endothelial cells were found on both sides of the median line. (a) At the level of the isthmus, the most prominent cyst of softening is on the left side, is of crescentric shape, measures 5 x 2 mm., and cuts some of the fibers of the pyramidal tract as well as some commissural fibers. (b)

A second but smaller cyst cuts various pyramidal fibers on the right side at the level of the isthmus, together with many of the deep commissural fibers of the pons. (c) The left brachium pontis is interrupted by an oval cyst, 1 x 0.4 cm., running downwards and outwards almost to the pia-mater. (d) Smaller cysts and vacuolar perivascular spaces occur elsewhere in the pontine region but no particular description of these is made for the present communication.

The case is evidently complex anatomically. The striking dural tumor had actually little to do with the physiology of the patient. The pontine arteriosclerosis must have had much more to do with pyramidal tract interference, although here again there is no massive destruction of either tract. The right-sided tract above the decussation is obviously smaller than the left-sided tract.

An investigation by the Nissl method of the cell pictures of precentral gyri shows that, in the blocks examined, the Betz cells are, with few exceptions, absent on the right side, and present, though reduced in numbers, on the left side. The presence of the tumor on the left side of the cerebrum has effected very little stratigraphic alteration of the underlying cortex. It is not possible to say what is the origin of the disappearance of the Betz cells from the right precentral gyrus. Possible factors seem to be toxic, from the meninges, arteriosclerotic, or secondarily degenerative.

In view of the equivocal character of the various intracranial lesions, including: (1) alterations of the Gasserian ganglia, (2) chronic and subacute meningitis over various parts of the cerebrum, (3) dural tumor of the left frontal region, (4) multiple cysts of softening of the pons,, (5) Betz cell atrophy more marked in the right precentral gyrus, it was hoped that the spinal cord findings would clear up the case. The spinal meninges, however, showed an extensive subacute inflammatory process with areas in which the lymphocytes have invaded the cord tissue. The areas of myelitis are chiefly in the periphery and are tolerably extensive in some levels, notable in the thoracic region of the left side. It is quite plain that the meningomyelitis, however recent it may have been, must have modified clinical symptoms through compression of the spinal roots.

The pyramidal tract degenerations in their intraspinal course are about equal on the two sides, so far as can be made out in Weigert preparations. In some levels, by means of neuroglia stains, it can be made out that the left pyramidal tract is traversed by more numerous neuroglia trabeculæ. The diagnosis of more extensive left-sided pyramidal tract lesion in the cord is based rather on neuroglia findings than on myelin sheath findings.

ANATOMICAL SUMMARY.

Acute and Subacute Lesions.

Acute fibrinous pericarditis. Acute degenerative nephritis.

Otitis media (bacillus of B. coli group).

Granulomata, possibly tuberculous, of Gasserian ganglia.

Subacute cerebrospinal leptomeningitis.

Focal encephalitis, by extension from meninges, especially beneath ependyma of posterior cornua of ventricles.

Focal myelitis, especially on the right side in the thoracic region.

Chronic Lesions.

Chronic interstitial nephritis, with atrophy of left kidney.

Slight arteriosclerosis, especially pontine.

Multiple cysts of softening of pons.

Chronic cerebral leptomeningitis.

Betz cell atrophy of precentral gyri, especially right.

Dural endothelioma with lime deposits.

Slight focal cerebral atrophy underlying tumor.

General cerebral atrophy with compensatory oedema of pia mater. Cystic septum lucidum.

CLINICAL SUMMARY.

It is extremely difficult to ascribe the various symptoms to definite lesions. The pontine lesions are of such a degree that they might easily modify any symptom which could ordinarily be ascribed to the tumor or the meningitis.

A tumor in the frontal region rarely, if ever, gives definite localizing symptoms. In this case the apathy and indifference to her surroundings and also the early headache may be due to it. Its position near Broca's convolution suggests some connection with the speech defect but it is more probable that the lesions in the pons have more to do with it.

The ptosis may be accounted for by the extension from the Gasserian ganglion but it seems very probable that there may have been a nuclear lesion. The visual hallucinations may be accounted for by the meningitis and the dulling of consciousness following it and the tumor.

The lesions in the pyramidal tract explain the Babinski reflex but there hardly seems to be enough difference in the two tract lesions to explain why it should exist on one side and not on the other. There was probably some focal lesion in the cervical cord which interfered with the reflex arc of the left arm and slightly with that of the right which could explain the arm reflexes.

The paralysis of the left side was due directly to the destruction of the Betz cells and this destruction can be accounted for by toxic influences from the meninges or by pressure from the tumor but one would be inclined to give more to the toxic hypothesis.

The case offers nothing new as far as localization is concerned but it does call attention to the vast changes which may be caused by arteriosclerosis and also to the meningeal consequences of a chronic otitis media. In a large number of the cases which have come to autopsy in this institution in the last six months pus has been found in the middle ear. There is no doubt that the middle ear infection has in some cases influenced the clinical picture. The diagnosis of such cases is almost an impossibility as yet but it is worth while to keep such things in view especially as they influence so much the prognosis.

MELANCHOLIA WITH DELUSIONS OF NEGATION: THREE CASES WITH AUTOPSY

BY H. W. MITCHELL, M.D., AND E. E. SOUTHARD, M.D.

Reprinted from THE JOURNAL OF NERVOUS AND MENTAL DISEASE, MAY, 1908.

MELANCHOLIA WITH DELUSIONS OF NEGATION: THREE CASES WITH AUTOPSY[1]

By H. W. Mitchell, M.D.,

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While engaged upon a more general analysis of involution-melancholia, presenile insanity, and allied conditions, our attention was arrested by three cases of melancholia showing feelings of unreality. Recent interest has been so great in patients with feelings of unreality and nihilistic delusions that we have been tempted to anticipate our more general report upon the great subsenile group with a particular account of these three cases. The cases present a certain uniformity both from a clinical point of view and from the histopathological side. Anatomically, the cases belong in the catalogue of insane subjects with " normal " brains or brains with " unimportant " or " trifling " lesions. It is these cases which now deserve the closest histopathological attention, especially from the point of view of the intracellular pigments and fats and their distribution. The problem in these cases of " normal " brains might shift from considering foci of destruction to determining the degrees and loci of intracellular clogging with pigments and fats.

The paper deals with three cases of melancholia which showed feelings of unreality and nihilistic delusions, but is not to be taken as a brief for Cotard's syndrome as an entity among mental diseases. Nevertheless, feelings of unreality and nihilistic delusions, together with various other ideas of a metaphysical cast, are so striking an element in certain conditions of melancholia that we can hardly escape throwing such cases into a group for convenience at least. Moreover, although delusions of this type undeniably dwell in the minds of many persons in and about the climacteric era and although the climacteric state appears to have many features which are met again and again and afford some color to the claim of melancholia as an entity, we do not wish at present to concede that either Cotard's syndrome or melancholia at large is an ultimate group for a finished psychiatry.[2]

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[1] From the wards and laboratory of the Danvers Insane Hospital. The term melancholia is here used in the older Kraepelinian sense.

Histopathology can have little to say on the cerebral side so long as the metabolism of involution presents such meager data. The present cases, however, so far as their examination was carried, offer interesting data which support the claim of a central rather than a peripheral disorder as the basis for the mental states shown. Moreover, the central disorder appears to involve, not so much the great cells which are related to the periphery, as the smaller cells which must be concerned with the elaboration and transforming of peripheral data.

Should our hypothesis hold, the cases of so-called melancholia (including many of those which fall into Cotard's syndrome) might prove to be founded on a central disease. The importance cannot be denied of proving that these patients are not simply explaining and rationalizing their own perverted metabolism, but are actually suffering from a fault in the very mechanism of explanation and rationalizing. Naturally the cerebral fault may itself turn out to be metabolic. We can have nothing to say on this line and offer our cases as preliminary to a more extensive study of the group called melancholia.

CASE I.—G. E. H. Admitted to Danvers Insane Hospital July 10, 1903. Age, 49. Occupation, clerk.

Family History.—His father was an eccentric, incapable man, and there was a history of occurrence of insanity in distant relatives on paternal side. The relationship and character of mental disturbance could not be ascertained.

Personal History.—Naturally, he was a man of cheerful, pleasant temperament, with average business capacity. His habits in regard to alcohol were good. There was no history or evidence of syphilis. Previous to present illness he had had lumbago on several occasions, but no well-defined attacks of rheumatism or any other disorder which could account for the cardiac hypertrophy found on admission. The occurrence of previous mental disturbance was denied by relatives. During the winter of 1902–1903, he lost money, became depressed, slept poorly, lost weight and had to give up work in February, 1903. His depression deepened and he became restless and agitated, fancied that he was ruined and in a hopeless condition.

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[2] Since this paper was first presented, Dreyfus has published "Die Melancholie ein Zustandsbild des manisch-depressiven Irreseins," 1907, representing a reversal of Kraepelinian opinions concerning melancholia as an entity.

He was admitted to the McLean Hospital, April 28, 1903. We are indebted to Dr. Tuttle for clinical notes which have been used in the case description. Upon admission at Danvers examination was made by Dr. H. M. Swift.

Physical Condition.—July 11, 1903. His muscular development was good, but he was poorly nourished. Area of cardiac dullness was enlarged to the left, and apex beat was in sixth space. There was a systolic murmur heard most plainly at the apex and transmitted to the axilla. Pulse was 90–100, increased tension, and radials were somewhat thickened. Urinary examination was negative. Cranial nerves were normal. Pupils equal and reacted to light. Tendon reflexes were lively and equal. No disturbance of sensation was found.

The notes on the mental condition from April 28 to July, 1903, are as follows: During the month of May there were short periods when orientation for time and place was imperfect, and at these times he had imperfect memory and displayed great agitation. He was distinctly apprehensive, thinking the register was a machine to kill him; that he had signed away the whole United States; that he had opened all the asylums in the United States; that he had killed his wife and could see her blood on his hands. At times, he appreciated the absurdity of these ideas and would converse clearly. Gradually his apprehensiveness and agitation increased, though at intervals he would demonstrate a good grasp upon surroundings. He became resistive, talked in anxious whispered tones between moans and sighs, and developed the feeling of unreality, seated, rocking body to and fro, wringing his hands; he would whisper between his groans and sighs: "I am all mixed up. It's all a mistake. I'm not Mr. H——. I am all gone, I am dead to the world." Again he would say: "I'm not G. E. H., I ought to be him, but I've taken these names along when I have seen them in the yard. I've made myself as Gibbs, I've been here as G. E. H., and have a home in Haverhill; not I, but G. E. H., has a home in Haverhill. I've made myself a different one."

His agitation increased, and he became untidy and very resistive. His productions became desultory and disconnected. He denied identity, had no stomach, could not take food, and at the last had no idea of time or place. He died of pneumonia July 13, 1903.

Summary of Case I.—Father was eccentric and there were instances of insanity on paternal side of family. Age, 49. Habits exemplary. Loss of money only recognizable cause for gradually increasing worry and depression. No serious illness previously. Cardiac hypertrophy, arterio-sclerosis, only recognized physical ailments.

Mental symptoms appeared in following order: worry, insomnia, restlessness, depression, delusions, possibly visual hallucinations, agitation, ideas of negation and stuporous condition preceding death. Orientation fairly well preserved until the last few days.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett and showed death due to pneumonia of the right lower lobe, lower portion of upper lobe, and posterior portion of the middle lobe of left lung. The heart muscle was pale and flabby. The mitral valve was moderately thickened. There were a few patches of atheroma in thoracic portion of the aorta. The liver showed slight surplus of fat. The heart weighed 445 grams. There was a chronic fibrous peritonitis in the region of the appendix and upon the lower surface of the liver and around the gall-bladder. Examination of the skull showed the sutures preserved and the diploë in large amount. The dura mater firmly adherent to the calvarium. The brain with pia mater weighed 1445 grams. The pia mater contained considerable fluid and was hazy along the edge of vessels. Adhesions were found at the bottom of the fissures of Sylvius. The large blood vessels at the base showed some yellow atheromatous patches of irregular distribution. The lumina of the arteries were not diminished. The choroid plexuses showed a few minute cysts. There were no focal areas of softening in the brain. The ependyma of the ventricles was smooth.

Microscopical Examination.—Several regions of the cerebral cortex in both hemispheres showed an essentially normal layering (Nissl's method). There are nowhere focal destructive lesions. One lesion is common to all the sections examined, viz., a great quantity of pigmented cells in the adventitiæ of the vessels in all parts of the gray and white matter (best demonstrated in Heidenhain iron hematoxylin preparations). The pigment around the larger vessels is enclosed in cells of the usual meningeal phagocyte type. But about the capillaries of the gray matter the pigment is as a rule enclosed in neuroglia cells.

The source of the perivascular pigmentation cannot be made out from the vessels affected, since all the vessels with but few exceptions are equally invested with pigmented cells. The distribution of pigment in neuroglia cells is a little more characteristic. The pigmentation of neuroglia cells is not, as in some conditions, particularly found in the outer or subpial layer or in the inner or fusiform cell layer. The neuroglia cell pigmentation tends to affect the intermediate layers of the cortex. This is best shown in the layers of large and small stellate cells of the calcarine areas. The frontal areas, however, show a fairly general distribution of pigmented neuroglia cells.

The nerve cell pigmentations are more characteristic in point of distribution. The large pyramidal cells of the frontal cortex are practically all pigmented and, in most cases, somewhat characteristically along the lateral borders and at the inferior angles, leaving the perinuclear region and the apical portion free of pigment. The pigment is not collected in a single sac, but appears to occupy interstices of the cells with perfect maintenance of their proper contours. The characteristic unifocal collections of pigment in the Betz cells of the paracentral lobules are absent in this case. The Betz cells have little or no pigment of any sort. The larger nerve cells (including the solitary cells of Meynert) of the calcarine areas fail to show much pigment.

The examination indicates a steady outward stream of pigment materials from the nerve tissues to the perivascular region. So far as the examination of a limited number of areas is conclusive, the autochthonous pigmentation of the nerve cells is maximal in cell types whose function is either unknown or receptive. Large elements like the Betz cells and the solitary cells of Meynert fail to show marked pigmentation. These larger elements are doubtless more directly related with the projection system than the others.

Case II.—T. H. Admitted to Danvers Insane Hospital June 13, 1904. Age, 75. Occupation, mason.

Family History.—Both maternal and paternal relatives were unusually healthy, long-lived people. His mother died at the age of 63, and had exhibited a continuous, melancholy depression for the last few years of life. One brother died of apoplexy at the age of 52. Family history was otherwise negative.

Personal History.—He had a normal development and became a capable and modestly successful contractor, retiring from business at the age of 65, with a small competency. His temperament was cheerful and sociable. Family relations were pleasant. At no period of life had he ever used distilled liquors, but occasionally he drank a little beer with meals.

At the age of 25, he had a venereal lesion, probably nonspecific. Aside from an attack of pneumonia seven years prior to commitment, he had always been healthy. His relatives had noted some memory failure for recent events during a few years before admission, and he had been troubled with insomnia for one year, but no symptoms of insanity were recognized until the week before his commitment. The loss of an only son eight years before, who left a widow and four children dependent upon the patient for support, had been the only known cause for worry. A sudden depression developed. He thought he had lost all his property and that he was responsible for the consequent misery of his family. He became sleepless for a week and finally cut his throat, wounding the larynx. He struggled to prevent dressing of the wound, declaring that he did not want attention, that he must die; and threatened to accomplish suicide by some other means. He was soon admitted to the hospital.

Physical Condition.—He had a powerful muscular development, was well nourished, tissues showing very little senile atrophy. There was an infected wound involving larynx. Temperature on admission 99.4°. There was harsh respiration and occasional coarse rales were heard over anterior surface of chest. Area of cardiac dulness slightly enlarged. Second aortic sound was sharp and accented. First sound at apex was roughened. Pulse was 126, fair tension, irregular rhythm and occasionally intermittent. Superficial arteries were thickened and tortuous, and there was well-defined arcus sensilis. Urine showed trace of albumin. No sugar. Sediment contained hyaline casts, pus cells, uric acid and calcium oxalate crystals. Strength was little impaired and he had perfect control of muscular movements.

Cranial nerves were normal. Pupils were responsive to light. Tendon and skin reflexes were normal. No sensory disturbance detected.

Mental Condition.—At time of admission, he was oriented for time, place and persons, and appreciated the character of his surroundings, but answers had to be obtained between his groans and protestations. His mental distress and agitation rapidly became more pronounced, and he would pace about his room, wringing his hands, his features contorted with emotion, muttering about his "most miserable state," his family and his deplorable acts. With great and steadily increasing difficulty his attention could be gained momentarily, but most of the time he took little notice of requests and struggled blindly against efforts to care for him. His spontaneous talk showed great depression, nihilistic delusions with the feeling of unreality; *e. g.*, "Oh! I am in a hopeless state. It is awful and nobody ever suffered this way. This is not a reality. This is eternity, this is eternity. Why such a thing as I the world never knew, the world never saw. Why! Why! Why! I can't move, I can't die." As nourishment was offered he said: "No, no, I can't take it. It won't do me any good. I can't take it, I am not a reality." At another time, he declared he was in a vault, and that the sunlight, streaming into the room was not real; that the sky was not blue; that the view from his window was not a reality; that the people about him were not real human beings, and that no person had ever been in such a miserable state as himself. His agitation was practically continuous. He would appear exhausted and lie down and secure short, fitful sleep. The suppurating laryngeal wound eventually, prevented audible speech, and death resulted from pneumonia on the eighth day in hospital.

Summary of Case II.—Mother had mental depression during last four years of life. Brother apoplectic. Age, 75. Moderate beer drinker. Old age and worry over loss of son and responsibility of caring for son's family only known causes for a comparatively sudden outbreak. No known illness, excepting pneumonia, seven years previously. Arteriosclerosis, nephritis, myocarditis and bronchitis from wound in larynx were the only physical ailments noted. Slight memory failure and some insomnia preceded for some months a sudden depression, painful delusions concerning self and family, suicidal attempt, great motor agitation, feelings of unreality largely confined to external objects, and nihilistic ideas. Orientation fairly preserved to the last few days of life.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett and showed death probably due to hypostatic pneumonia. Suicidal wound of neck. The heart was fatty. Arteriosclerosis was general, involving the aorta and in particular the splenic vessels and the arteries of the base of the brain. There was well-marked chronic diffuse nephritis. Examination of the head showed the following: dura mater completely and firmly adherent to the calvarium. The pia mater free from thickening. Basal arteries beset with scattered foci of yellow thickening. Internal carotid arteries notably stiff and yellow. Small old cyst of softening just outside tip of posterior horn of right lateral ventricle. The brain with pia mater weighed 1,300 grams.

Microscopical Examination.—The frontal, paracentral and calcarine regions of the cerebral cortex show essentially normal layering. The most prominent feature is a universal pigmentation of perivascular cells, neuroglia cells, and nerve cells of about the same degree in all regions examined. The pigmentation about the vessels is by no means maximal, and is of a degree often shown in younger subjects under different conditions. The neuroglia cell pigmentation affects practically all the cells and, since it occurs also in the subpial layer, is probably due to fiber degeneration as well as to nerve cell changes. Satellite cell pigmentation is, however, also frequent and characteristic, so that a nerve cell origin for some of the pigment is highly probable. The examination of the nerve cell pigmentation is facilitated by parallel study of adjacent sections stained by Nissl's methylene blue method and by Heidenhain's iron hematoxylin method. By Nissl's method it is easy to make out the universality and extent of the senile yellow pigmentation in the layer elments, *e. g.*, large pyramidal cells, Betz cells, solitary cells of Meynert. Besides the yellow pigmentation of the banal type shown in old age, the Heidenhain preparations show an extensive development of pigment staining black by this method. This latter black-stained pigment lodges in the nerve cells of the intermediate layers, but characteristically affects the smaller elements, *e. g.*, small pyramidal cells, as well as also the large pyramidal cells (in which the black-stained pigment accompanies the yellow pigment which remains unstained). The Betz cells and the solitary cells of Meynert, despite their accumulations of or distention with yellow pigment, fail to show more than a very few black globules in the Heidenhain preparations. The black-staining pigment seems never to alter the cell form, but to lie in crevices which may represent lost tissue. The Nissl stain shows that the Nissl bodies are throughout not well stainable; but this circumstance cannot yet be unequivocally related to the cell pigmentation.

The arteriosclerotic element in this case is not prominent, despite the old cyst of softening in the left occipital region. Nor is cerebral atrophy a prominent feature. The most striking features are extensive pigmentations, which are partly of senile origin and partly reside in elements which are of unknown or receptive function. These two types of pigmentation are easily separable in the Heidenhain preparations.

CASE III.—J. H. A. Admitted to Danvers Insane Hospital, November 21, 1903. Age, 65. Occupation, shoemaker.

Family History.—Patient's father died of some cardiac disorder at age of 77. His mother died at the age of 67, after suffering from senile dementia for over three years. One brother died of tuberculosis. The history concerning grandparents and collateral branches was unobtainable.

Personal History.—Nothing was known of early life. He enlisted in the army, serving three years during the Civil War, and was afterwards employed as a shoe-factory operative. He was married in 1873, and has two healthy adult children. His wife stated that he had been industrious, kind to family, pleasant and agreeable in disposition. Since early life he had been a moderate user of tobacco and alcohol. He was not a daily drinker and was never known to have been intoxicated.

He had had a purulent discharge from the right ear following scarlet fever at the age of three. This was the only severe illness he had had until the age of 61, when he had typhoid fever and la grippe during the same year and was mildly delirious during both illnesses. He made good recoveries and worked steadily until nine weeks before his commitment, when he was discharged for failure to perform work properly. For two or three months previous to this event he had slept poorly, lost weight, worried over trifles, and had shown evidences of mild hypochondriacal depression. Following the loss of his position, mental symptoms had been progressive. He began to think that he and his family would starve and freeze, and was greatly distressed by fancied physical ailments; *e. g.*, he had the idea at one time that his head, eyes and limbs were growing large and later thought that he had become much smaller than others who were correspondingly increased in size. Occasionally he would seem to have some insight, and he lost weight steadily. He never showed any suicidal tendencies. A sudden threat of violence to members of his family and refusal of food were the immediate causes of his hospital commitment.

Physical Condition.—He had slender muscular development, pallid complexion and was poorly nourished. His skin was dry and wrinkled. He had sordes on lips and teeth, tongue was coated and breath foul. Temperature ranged from 99° to 100°. Area of cardiac dulness was not increased. Second aortic sound was sharp and accented, and first sound at apex was roughened. Pulse was 96, feeble volume and irregular rhythm. Arteries were soft. There was a faint arcus senilis.

Abdomen was shrunken. Urine was turbid and had a foul odor. Acid. Sp. gr. 1013. No sugar or albumin present. Sediment showed squamous epithelial cells, few red corpuscles, bacteria and moulds. He had accurate control of muscular movements, and walked with a firm gait. He could hear faint watch tick with left ear and could read coarse print. The right pupil was slightly larger than left, and both reacted promptly to light. Tendon reflexes were generally hyperactive and equal. Sensory tests were of little value, as he declared that he had no feeling, although wincing at pin pricks.

Mental Condition.—Soon after admission, he objected to every effort to care for him. He refused to walk, said that he had no legs and could not stand; when an attempt was made to raise him from a sitting position he doubled up his limbs and shouted protests against the cruelty of trying to make a man with no legs walk. His enunciation was not impaired and he talked freely, excepting that he would refuse to answer some questions and remain mute for a short time. In answering questions to test orientation, grasp on surroundings and retention of school knowledge, he would give correct replies after protests, refusals, and nihilistic statements; *e. g.*, Q. Where are you? A. "I don't know, I've got no brains. Yes I do too, Danvers. I've been here. Down here for insane and you are going to report I am all right." Q. Are you sick? A. "Course I am, and you know it. I've got no brains and I can't talk and you are going to make out the wrong report. I've got no heart and no stomach, and I can't swallow. I haven't any feelings." His tones were sharp and manner petulant. He was apprehensive and showed some agitation. There was no evidence of retardation. After much urging he would swallow liquid nourishment in great quantities, but saying it did him no good, because he had no stomach, nothing but a hole and he would drink to fill that up. Every question would suggest some new idea. When asked if he knew any people about him, he answered: "Yes, you are all great big men and so strong, you must weigh over 400 pounds, and I'm so small you can't see me. I'm freezing to death and you cover me up with great, heavy, wet blankets. I wouldn't burn if you threw me in the hottest furnace, but I can't suffer because I've got no brains."

He would say that he could remember nothing of events from day to day because he had " no brains " and in the same sentence make remarks that showed partial recollection. Depression was constant and at times was very marked. During the first week in hospital he was restless, walking to and fro in his room, groaning and picking at his clothing and fumbling with his bedding. He was occasionally untidy in habits. With increasing weakness, his ideas of negation and unreality became more absurd, and were more brokenly expressed. Death occurred December 19, 1903.

Summary of Case III.—Mother died of senile dementia at 67. Moderate use of alcohol. Age, 65. No assignable cause for insanity. Typhoid and la grippe with delirium accompanying both disorders, four years previously.

Emaciation, arteriosclerosis of mild degree, nephritis, cystitis and lively reflexes were the only important physical ailments. Mental symptoms gradual in onset. Slowly increasing hypochondriacal depression, with incapacity for work, was noted for four months before evolution of ideas of unreality and nihilistic delusions. Mildly agitated, petulant and complaining during the last. Orientation and memory quite well preserved.

Autopsy Findings.—The autopsy was performed by Dr. A. M. Barrett, and showed an extensive suppurative process in the retroperitoneal tissue around the bladder with abscesses anterior to the bladder and numerous narrow sinuous pus channels running backward on either side of the bladder. The process extended upward beyond the limits of the pelvis into the perinephritic fat tissue as far as the upper poles of the kidney.

The right auricle of the heart showed numerous small thrombi. There were numerous recent emboli in the primary branches of the left pulmonary artery. The aorta showed, 30 cm. below the arch, a large thrombus with puriform softening. The spleen had failed to react to septicemia. The lungs, pancreas, renal pelves, ureters and bladder showed various signs of acute inflammation. Moderate aortic sclerosis. The brain showed no gross signs of alteration at the autopsy and was hardened for four weeks in ten per cent. formaldehyde solution. More careful examination later also proved negative. The ependyma of ventricles was smooth.

Microscopical Examination.—Cultures from the heart's blood and retroperitoneal pus showed pneumococcus and a bacillus, probably bacillus coli communis. Examination of the organs of the trunk added little to the gross findings. The kidneys showed a mild chronic interstitial change with slight fatty changes in the epithelial lining of the tubules.

Microscopical examination of the various regions of the cerebral cortex by Nissl's method, by L. Ehrlich's pyronin method for plasma cells, and by Heidenhain's iron hematoxylin method demonstrated a moderate and in places quite trivial accumulation of cells of the lymphocyte group in the sheaths of small vessels in the lower layers of the gray matter and the adjacent white matter. This accumulation of lymphocytes (and plasma cells) is strikingly even in degree in the parts examined (left and right superior frontal, left and right paracentral, left and right calcarine and occipital regions) and in most sections has to be sought with some care. There is no noteworthy alteration of the nerve-cells, if we except pigmentation of the larger elements (large pyramidal cells of frontal area, Betz cells, large pyramidal cells of occipital area). The other nerve elements (in particular the solitary cells of Meynert) fail to show pigmentation. Numerous neuroglia cells, as well as cells applied to the walls of capillaries, are well pigmented (seen especially in the Heidenhain preparations). The cell layers of the cortex and the cell arrangements of the white matter show no notable alteration.

The question arises whether the data admit the diagnosis *general paresis.* A strict histological diagnosis might be chronic degenerative and exudative encephalitis of a diffuse but mild nature with the exudative element slightly predominant.

SUMMARY OF POST-MORTEM FINDINGS.

The causes of death were: Case I, pneumonia; Case II, pneumonia following suicidal wound of neck; Case III, general infection from pelvic suppuration.

All three cases presented more or less sclerosis of the aorta. The senile case (II) and case I showed considerable sclerosis of the large arteries of the base of the brain.

Aside from a small old cyst of softening in case II, no brain showed focal destructive lesions. No brain gave sign of general or focal atrophy upon macroscopic examination. Case I was the only case to show pia mater changes, and these were confined to haziness along vessels and adhesions at the bottoms of the Sylvian fissures. Case III, despite the chronic exudate found upon microscopic examination, showed no macroscopic alterations of the pia mater. The ependyma was in all cases smooth.

Microscopical examination of three or more areas in each hemisphere was carried out by several methods, notably by Nissl's original methylene blue method and by Heidenhain's iron hematoxylin method.

Common to all the cases is an accumulation of meningeal *phagocytes containing pigment.* This perivascular pigmentation is of about the same degree and quality as that found in most adults beyond the age of fifty years. Whether perivascular cell pigmentation signifies increased wear and tear on the part of the nervous tissues, or whether it rather signifies a reduction in the serum's power to take up these substances cannot yet be told with assurance.

A second common feature of the cases is *neuroglia cell pigmentation.* Whether the collections of pigment (or of fat-like bodies) here shown indicate phagocytosis on the part of these cells cannot be established. The accumulations of fat-like substances might be due to some neuroglia cell activity affecting materials brought to the cells in solution. The senile case showed well-marked satellite-cell pigmentation. The neuroglia-cell pigmentation which is found common to all three cases is pigmentation of the scattered neuroglia cells of the middle layers of the cortex.

The nerve cells also show deposits of pigment or fat-like substances. The Heidenhain preparations bring out the presence of two kinds of pigment, which can be distinguished according to capacity or lack of capacity to take up the hematoxylin. The type of pigment which fails to take up hematoxylin is collected in the familiar yellow sacks which form unifocal deposits in the cytoplasm of the larger cells. This yellow pigmentation is found in case II, as it is in numerous senile and subsenile conditions. It is this pigment which is so common that histologists attach little significance thereto. The other kind of pigmentation, so well demonstrable by the Heidenhain method, is developed in all of our three cases. It is in this pigmentation, if in any feature now demonstrable, that we must look for somewhat differential characters in diseases of the group under discussion. The most significant feature of this type of pigmentation is its plurifocal distribution in the affected cells. Whereas the yellow sacks of the more banal type of pigmentation seem to enter into no intimate relation with the cell and may not interrupt its paths, the plurifocal pigmentation, on the contrary, is so distributed that it may well modify or influence the progress of impulses through the cells. It may be noted that this kind of pigment is apt to be deposited at the sides and inferior angles of the cells (*e. g.*, of the large pyramidal cells of the frontal cortex) and to neglect the perinuclear and apical portions of the cells.

If we take into account the iron-hematoxylin-staining pigment and leave out of account the banal yellow pigment, it appears that the larger elements (*e. g.*, Betz cells, solitary cells of Meynert) are not likely to be affected. The iron-hematoxylin-staining pigmentation proves to be maximal rather in those elements whose function we do not understand or term receptive. If this pigmentation can be taken as a sign of central disease, the disease appears to involve not so much the larger elements which come into immediate relation with the projection system as the smaller elements having to do with transference of impulses or having unknown functions.

General Summary and Remarks.

The disease group melancholia has a somewhat precarious footing in present-day psychiatry. The purest cases appear to occur in or about the climacteric era. The practical alienist is always reluctant to place a case in the group melancholia, lest it shortly transpire that the case should rather have been counted senile, or arteriosclerotic, or, in some other way, frankly organic. Moreover, it frequently appears that error may creep in the opposite direction and the patient, alleged to have melancholia, turn out to be actually a victim of some constitutional defect or of some acute psychosis.

We have found difficulty in resolving our ideas about the disease group melancholia and were for a time inclined to believe that any given case could perhaps be transmuted, as a matter of diagnosis, into some other group.

As a beginning in this group, we have here introduced three cases which, whether they fit any acknowledged grouping or not, appear to have certain features in common as well as certain instructive differences. The psychological color and, to some extent, the course of these cases recall some features of Cotard's syndrome.

In every case there were a few established instances of insanity in the direct line on one or other side. The hereditary features, interesting in each case, appear to have little in common, except the terminal continuous depressions in the mothers of two patients (cases II and III).

The lives of the three patients showed little which can be regarded as underlying their ultimate conditions. Case I used no alcohol, Case II drank beer with meals, Case III used alcohol moderately. Venereal history practically negative in all cases.

Occupations: clerk, I; mason, II; shoemaker, III.

Previous diseases: lumbago, I; pneumonia seven years before commitment, II; scarlet fever and purulent otitis media, æt. 3, and typhoid fever and la grippe with delirium, æt. 61, III.

Ages at onset: 48, I; (69) 75, II; 65, III.

Durations: 8 months, I; (8 years) 2 weeks, II; 24 ca. weeks, III.

Onset: gradual, I, III; sudden, II.

Assignable causes: financial worry, I; senility and domestic worry; nothing, æt. 65, III.

Physical conditions: arteriosclerosis in all cases; case III showed emaciation, nephritis, cystitis, increase of reflexes.

Mental states: ideas of negation in all cases, developing in case I after slowly increasing depression and agitation with delusions about self and family and questionable hallucinations; in case II, after gradual senile failure, as sudden deep depression with agitation, delusions of ruin of self and family, and suicidal attempt; and in case III, after slowly developing hypochondriacal depression.

The feelings of unreality and ideas of negation presented a certain variety in the three cases. Case I showed an alteration of personality, uttered frequently in such phrases as "I'm all gone, I'm dead to the world. I'm not G. E. H. I've made myself as Gibbs; I've been here as G. E. H." Case II showed a feeling of unreality, both as regards the outer world ("sunlight not real, sky not blue. people not real human beings") and as regards himself ("I can't move; I can't die"). Case III showed an alteration of point of view as to the outer world ("you're all great big men, and so strong; you must weigh over 400 pounds") and nihilistic ideas ("I am so small you can't see me; I've got no brains; and I can't talk; I've got no heart, and no stomach, and I can't swallow; I wouldn't burn if you throw me in the burning furnace").

The anatomical side of these cases presents several common aspects, but little which promises to explain the disease. Arteriosclerosis, when confined to the large branches of the circle of Willis, can scarcely be invoked as underlying symptoms of such specialized character as those under consideration.

Just as the patients showed strikingly little in alterations of reflexes (increase in case III), so the brains showed strikingly little in the shape of gross or focal alterations (small old cyst of softening in case II and mild chronic exudative process in case III).

Moreover, the brains gave little evidence of general or focal atrophy. No striking alterations in cortical topography and arrangement of layers could be detected on microscopic examination. Pigment-bearing cells in perivascular spaces were constantly found; and, in default of any suspicious localization of these, we must attribute them rather to the results of advancing years than to a special factor.

Neuroglia cell pigmentation was also quite constantly found; but this was not so universal in distribution as was the case with the perivascular cell pigmentation. Common to all three cases was a neuroglia cell pigmentation in the intermediate layers of the areas of cortex examined. The relation of the neuroglia cell pigmentation to cortical activity could not be made out. Satellite-cell pigmentation was not constant.

Nerve cell pigmentation was constantly found in the elements of moderate size in all parts of the cortex examined. This pigmentation was strikingly brought out by the use of iron hematoxylin. The pigmentation in question has a somewhat characteristic locus in the affected cells, fails to destroy their contours, and lies apparently in interstices in the cells. This interstitial nerve cell pigmentation, as brought out by iron hematoxylin, is to be sharply distinguished from the familiar yellow sack pigmentation of the major elements.

Pending the increase of knowledge concerning the pigments and fat-like deposits in general, we can at least investigate their occurrence topographically. It seems to us that, however fragmentary the present findings are and however far we may be from bringing such findings into relation with disorders of apperception, we have at least a promising field for investigating the conditions of what seems to be a truly cortical disorder. We are at present at work upon accessible cases of melancholia.

A Case of Brain Abscess Showing the Pneumococcus.

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AMERICAN MEDICAL ASSOCIATION.
ONE HUNDRED AND THREE DEARBORN AVENUE.
CHICAGO.

A CASE OF BRAIN ABSCESS SHOWING THE PNEUMOCOCCUS.*

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BOSTON, MASS.

In THE JOURNAL of the American Medical Association for Jan. 6, 1906, Drs. E. E. Southard and C. W. Keene reported a series of "twelve cases of human brain infection with the pneumococcus, together with the results of inoculation of the pneumococcus in the brains of guinea-pigs." The following is a report of another similar case, showing some points of especial interest, with an abstract of previously reported cases of pneumococcic cerebral infection collected from the literature.

Drs. G. L. Walton and G. K. Sabine have kindly furnished clinical notes on the case. Dr. P A. Lewis made the bacteriologic cultures. The autopsy was done by Dr. E. E. Southard.

History.—Patient was an unmarried woman, 35 years old. Had had measles, scarlet fever and whooping cough in childhood. On Feb. 5, 1905, after riding in a trolley car, patient noticed a tingling in the right foot, followed by numbness extending to the entire right side, headache and gradual onset of right-sided motor paralysis, with dragging of the toe and difficulty in using the pen, slight aphasia and dulness of intellect. There was gradual improvement until March 5, 1905, when headache returned with aphasia, slight stiffness of the neck and temperature of 101 F., pulse of 70. At this time patient was seen in consultation by Dr. F. C. Shattuck, whose examination was negative otherwise than as concerned the paralysis. Her condition grew worse, with occasional vomiting and moderate leucocytosis. Seen in consultation by Dr. G. L. Walton on March 12, 1905, she had a normal fundus and no hemianopsia. She had rigidity of the neck, none of the back, and a suggestion of Kernig's sign on both sides. She talked freely and in a rambling manner, suggesting a low form of delirium. She showed paraphasia and could not name the days of the week or months of the year. She grew steadily worse and died April 11, 1905, with moderately high temperature toward the end.

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* From the Pathological Laboratory of the Harvard University Medical School.

Clinical Summary.—Gradual onset of right-sided sensory and motor disturbance, with headache, slight aphasia and mental dulness. Slow course of disease with very marked remissions. After four weeks, onset of meningeal symptoms, with vomiting, fever and leucocytosis, progressing to death nine weeks and two days after first attack.

Anatomic Findings.—Fairly developed, poorly nourished woman with dark hair. Extremities rigid. Postmortem lividity of dependent parts. No edema. The walls and fluid of the peritoneal cavity were normal. Appendix normal and the mesenteric lymph nodes normal. The pleural cavities were normal, except for slight, easily separable bands at the apices. In the pericardial cavity were found several hundred c.c. of clear fluid without fibrin. The auricular cavities of the heart were distended with cruor clot. Heart walls, endocardium, valves, and coronary arteries normal. Both apices of the lungs, behind and below, showed small areas, less than 1.5 cm. square, of yellowish-brown fibrosis without caseation. Lung substance in general normal. Lower lobes behind were blood-filled and here and there showed ill-defined areas of lighter color and increased consistence. The bronchi were clear and the bronchial lymph nodes normal. The capsule of the spleen was fairly tense, the substance a trifle pulpy, the Malpighian bodies distinct and the trabeculæ normal. In the gastroenteric tract no lesion was found. The liver border was sharp and its consistence normal. Its color was slightly yellower than normal. The gall bladder and pancreas were normal. The kidneys stripped well, their blood content was high and substance normal. The ureters were normal. The adrenals showed central brown softening (postmortem). The aorta was normal.

The scalp and cranium were normal. Dural sinuses contained cruor clot. The dura was tense and the dural veins full. The arachnoidal villi were moderately developed. Subdural space was almost dry. The pia mater was congested, more over left hemisphere than over right. Convolutions were flattened, slightly more on right side. The basal pia mater was filled with slightly viscid, greenish, serous pus, which ran up along the Sylvian vessels a few centimeters. The under surfaces of the pons and medulla were bathed in pus. The velum interpositum and especially the sheath of the left anterior chorioidal artery were soaked in pus. The pituitary body was soft. There was no great amount of exudate about the optic nerves. On section the brain substance was everywhere moist and fairly firm. Puncta cruenta distinct. Both ventricles contained pus in the posterior cornua. The ependyma was moist and over the lenticular nuclei of a saltsprinkled appearance. The right ventricle contained more pus than the left. On section of the ganglia an abscess, 2 cm. in average diameter, was found in the left optic thalamus, communicating with the body of the lateral ventricle, but not with the third ventricle. The cavity was filled with pus similar to the pus in the basal cisternæ. The wall of the abscess was irregular and injected. There was a zone of reaction about it, 2 or 3 mm. in diamter, of a firm, opaque, pinkish-gray, injected tissue. The middle-ear cavities were both clean.

Anatomic Diagnosis.—Abscess of left optic thalamus and wall of lateral ventricle. Pyocephalus and ependymitis. Basal leptomeningitis. Early bronchopneumonia. Healed tuberculosis of apices.

Bacteriologic Finding.—Pneumococci were recovered from the abscess, but died on the first subculture.

Anatomic Summary.—A pneumococcic abscess of the left optic thalamus, with secondary pyocephalus, ependymitis, basal leptomeningitis and bronchopneumonia. Source and port of entry of infection not discoverable.

Microscopic Findings.—There were slight chronic interstitial myocarditis, slight arteriosclerosis of spleen and pancreas, moderate fatty infiltration of the liver, and in the kidneys slight general increase of interstitial connective tissue and cloudy swelling of the tubular epithelium. The lung showed focal areas of pneumonic consolidation, the exudate contained little fibrin, but consisted chiefly of polymorphonuclear neutrophiles, with a few large mononuclear basophiles and an occasional red blood corpuscle and large phagocytic cell. Within the latter, and scattered here and there in the exudate, were a few lanceolate diplococci. There were also large masses of staphylococci. The cerebral meninges were somewhat thickened and edematous, with some increase of connective tissue, but without exudate. They were, however, slightly infiltrated with polymorphonuclear and lymphoid cells. The subpial layer of neuroglia was neither wider nor denser than normal. The cortex showed slight edema and a few wandering polymorphonuclear and large mononuclear leucocytes. The subcortical tissues showed considerable general and perivascular infiltration with plasma and lymphoid cells and foci of more marked infiltration in which a differential count of the white cells showed the proportion: Lymphocytes, 66 per cent.; plasma cells, 20 per cent.; polymorphonuclear neutrophiles, 10 per cent.; large mononuclear cells, 4 per cent. There was also a considerable increase of connective tissue through this region, both interstitially and about the blood vessels. Gram-staining, capsulated, lanceolate diplococci were to be found freely in the infiltrated areas. The walls of the lateral ventricles showed slight general edema. There was scattering infiltration of the tissues with wandering individual leucocytes, and here and there, especially in the perivascular spaces, large areas and smaller foci of cellular aggregation, which gave average differential counts of lymphocytes 40 per cent., plasma cells 36 per cent., polymorphonuclear neutrophiles 20 per cent., large mononuclear cells 4 per cent. Among these cells were observed many lanceolate diplococci. There was considerable thickening of the subependymal layer of neuroglia. The ependymal cells appeared normal, but an occasional leucocyte could be seen pushing its way between them toward the ventricular lumen. In the ventricular cavity was a richly cellular exudate composed of polymorphonuclear neutrophiles 75 per cent., lymphocytes 15 per cent., large mononuclear cells 10 per cent.

The abscess was surrounded by a fairly thick and definite wall of fibrous connective tissue. In the adjacent areas there was diffuse cellular infiltration, particularly in the adventitia of the larger arteries, giving a differential count of lymphocytes 63 per cent., plasma cells 30 per cent., polymorphonuclear neutrophiles 5 per cent., phagocytes 2 per cent. Lanceolate diplococci were seen everywhere. The contents of the abscess consisted of necrotic material, pneumococci, and cells, the latter in the proportions of polymorphonuclear neutrophiles 65 per cent., lymphocytes 30 per cent., large mononuclear leucocytes 5 per cent.

The chorioid plexus showed granular coagulum and leucocytes caught in the villi. Lining cells were occasionally swollen, as a rule normal and supplied with large vacuoles. The perivascular tissues showed great numbers of plasma cells, some with two nuclei. In the same locus were cells with basophilic cytoplasm caught in mitosis. The cerebellum was normal in every respect.

In the medulla, the meninges were overlaid by an exudate consisting of considerable fibrin, with cells in the percentages, lymphocytes 83 per cent., large mononuclear cells 15 per cent., polymorphonuclear neutrophiles 2 per cent. The meningeal vessels were densely surrounded by similar cell aggregations. The spinal accessory nerves were not invaded by leucocytes. There was no neuroglial hyperplasia. There was slight sclerosis of the meningeal arteries. Pneumococci were present in them and in the exudate. The adjacent tissues of the medulla were but slightly infiltrated. In the olivary nuclei were many large ganglionic cells, some showing the axonal reaction.

In the cervical cord, the meninges were much thickened, with an exudate composed of lymphocytes 60 per cent., plasma cells 12 per cent., large mononuclear leucocytes 20 per cent., and polymorphonuclear neutrophiles 8 per cent., with very little fibrin. There was comparatively little increase of connective tissue, and little infiltration of the cord except in an area immediately surrounding the central canal, where there was also considerable increase in thickness and density of neuroglia. The ependyma was normal. There were no changes in the motor cells of the anterior horns.

Microscopic Summary.—Slight arteriosclerosis. General perivascular lymphocytic infiltration of nerve tissue. Walled-off abscess with contents of the usual cellular composition.

GENERAL SUMMARY AND REMARKS.

The case was characterized by cerebral symptoms and signs from the outset, subacute for the first four weeks, then increasingly acute till death after a total duration of nine weeks and two days. The points of especial interest in connection with it are two: First, the cellular proportions in the meningeal exudate and in the perivascular and general infiltration; second, the absence of determinable source or port of entry for the infection.

As is shown by the figures in the foregoing paragraphs, there was a marked predominance of lymphocytes and plasma cells in the infiltration of cortical tissue and ventricular walls and in the meningeal exudate, whereas in the abscess cavity, in the ventricular lumen, and in the pulmonary exudate, polymorphonuclear leucocytes prevailed. In this respect this case resembles numbers 1, 4, 7 and 16 in the series of Drs. Southard and Keene described in the article referred to above, but the preponderance of mononuclear forms was much greater than in any of them. There was distinct subpial and subependymal gliosis. Lanceolate diplococci were found freely in all the affected tissues, showing a generalized infection.

In each case of the Southard-Keene series some source for the infection is determinable: otitis media, trauma, acute or chronic pulmonary conditions, septicemia. In this case no such source could be found. The onset of symptoms was gradual, there was no antecedent injury or infection elsewhere. The pneumonic process in the lung was evidently terminal and secondary to the brain infection, which must be concluded to have been primary and coming either from the general blood stream or possibly through the nose.

With a view to comparing this case with others, and for the sake of completeness, I have attempted to collect from the literature all previously reported cases of pneumococcic cerebral abscess.

After careful and thorough search I have found reported only eight cases of cerebral abscess, in which the presence of the pneumococcus of Fränkel in the pus from the brain was demonstrated by bacteriologic examination. I have thrown out a number of cases of cerebral abscess following pneumonia, in which the presence of the diplococcus lanceolatus was not thus demonstrated but in some of which it doubtless was an etiologic factor in the production of the abscess. Following are the references and brief summaries of the eight cases in question:

1. Macewen:[1] An otitic cerebellar abscess of the left side, with a subdural abscess of large size situated above the tentorium, involving the posterior third of the two upper temporal convolutions, the angular gyrus, and a considerable portion of the adjacent occipital lobe. Both abscesses were opened and drained, with complete recovery. Pus from the subdural abscess contained pneumococci and staphylococci pyogenes aurei.

2. Sahli:[2] An abscess of the occipital lobe, with hemiopia, following an influenza otitis. Pus from the abscess and from the ear showed Fränkel's pneumococcus. The patient died, a few weeks after operation, of purulent meningitis proceeding from a small secondary abscess near the almost healed original focus.

3. Siron and Josué:[3] Multiple cerebral abscesses following influenza with bronchopneumonia. At the autopsy was found a subarachnoid abscess, communicating through the left temporal lobe with the ventricles, which were full of pus. There was also an abscess of the frontal lobe, one of the lenticular nucleus, one of each occipital lobe, and one of the lung. In all these the pneumococcus was found. The ears and sinuses were normal.

4. Boinet:[4] In this case there was onset of cerebral symptoms six weeks after recovery from influenza with bronchopneumonia. Death occurred five weeks later. At autopsy an abscess was found in the left temporal lobe, ruptured into the ventricle, with three subcortial diverticula. There was incipient meningitis. Pneumococci and streptococci were present in the pus. There had been destruction of the corpus striatum and part of the corona radiata. The middle ears were normal.

5. Boinet:[5] Five days after the sudden onset of cerebral and meningeal symptoms death occurred. At autopsy a purulent meningitis was found, especially at the base, and a small abscess in the corona radiata of the parietal lobe, pus from

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[1] Pyogenic Infectious Diseases of the Brain and Spinal Cord, Glasgow, 1893.

[2] Volkmann's Sammlung klinischen Vorträge, July, 1891, xxiii, p. 293.

[3] Presse méd., 1895, p. 235.

[4] Marseilles méd., xxxvii, p. 641.

[5] Rev. de Méd., vol. xxi, p. 113.

which contained pneumococci, staphylococci and streptococci. In the lungs there was hepatization at the base.

6. LANDRIEUX:[6] Death occurred on the fifth day from a lobar pneumonia, two days after the onset of cerebral symptoms with complete left hemiplegia. An abscess was found in the right hemisphere, occupying partly the lenticular nucleus, partly the anterior segment of the posterior arm of the internal capsule. It contained pneumococci in pure culture.

7. APERT and DELILLE:[7] After a fortnight's illness, there was sudden onset of meningeal symptoms, and death three days later. The patient, a girl of 14, had had bronchitis two years before, followed by a persistent cough. At autopsy was found dilatation of the bronchi, a pulmonary abscess, and multiple cerebral abscesses, one in the right prefrontal region, one in the left temporo-occipital, one in the left parietal lobe, and one in the right occipital lobe. All the abscesses contained pneumococci.

8. GRUENING:[8] A pneumococcus infection through the nose produced orbital cellulitis. At the first operation the orbit and the empyematous ethmoid cells and frontal sinus were drained. Cerebral symptoms ensued. A second operation exposed a large abscess of the frontal lobe, with a number of pockets, pus from which showed pneumococci. Pneumonia and pneumococcemia followed, with death in five days.

To these may be added the one case of the Southard-Keene series which showed an abscess.

9. SOUTHARD-KEENE:[9] Man of 25, with obscure history of previous head injury, had headache for four days and was unconscious two days. Death occurred six days later, ten days from onset of symptoms of meningitis. Autopsy showed cerebrospinal meningitis, with small focal abscess in the white matter opposite the left frontal cortex, encephalitis and pyocephalus. Cultures from heart's blood and brain gave pneumococcus.

These nine cases, then, with the one now reported, make a series of ten in which the pneumococcus is definitely determined as the infecting organism. Of these two (Cases 1 and 2) were secondary to otitis media, three (3, 4 and 6) to pneumonia, one (7) to chronic pulmonary condition, one (8) to nasal infection, one (9) to trauma, and two (5 and 10) to infection through undiscoverable sources. Case 5 was probably one of fulminating septicemia, leaving the present case (Case 10) as the only one of slow onset without demonstrable port of entrance for the infection. In this respect, and in the relative proportions of the cells in the exudate and infiltration, it is believed to be unique.

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[6] Jour. des Practic., 1903, xvii, No. 9, p. 129.

[7] Bull. de la Soc. anatom. de Paris, 1904, vi, p. 631.

[8] Med. Record, lxv, p. 215.

[9] THE JOURNAL A. M. A., 1906, xlvi, p. 16.

Attention is especially drawn, moreover, to the occurrence of lymphocytes and plasma cells in the various nervous tissues. The occurrence of such cells has been made the basis of extravagant claims by several German writers of the virtual specificity of the plasma cells in the meninges and perivascular tissues in general paresis of the insane. Those who maintain the virtual specificity of the plasma cell in paretic tissue charily admit, of course, that luetic and tuberculous tissues likewise exhibit local collections of lymphocytes and plasma cells. The same cells occur in the present case of pneumococcic abscess.

FURTHER STUDIES IN ANAPHYLAXIS

I. On the Mechanism of Serum Anaphylaxis and Intoxication in the Guinea-pig

II. On Recurrent Anaphylaxis and Repeated Intoxication in Guinea-pigs by means of Horse Serum

III. The Relative Specificity of Anaphylaxis

IV. The Localization of Cell and Tissue Anaphylaxis in the Guinea-pig, with Observations on the Cause of Death in Serum Intoxication

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FURTHER STUDIES IN ANAPHYLAXIS.[*]

I. *On the Mechanism of Serum Anaphylaxis and Intoxication in the Guinea-pig.*

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The hypothesis which we offered a year ago[1] as explanatory of the mechanism of the anaphylaxis in guinea-pigs, which follows an initial injection of horse serum, and of the intoxication which evidences this increased susceptibility, occurring on a second injection of the same serum, differs essentially from the explanations of other workers on this subject. While we in no manner wish to assert that the working hypothesis which we have employed does more than approximate the ultimate truth of this interesting condition or reaction of the animal body, our further study not only has convinced us that our explanation best agrees with the acquired facts, but that the opinion held by the majority of those who have attentively considered the problems of anaphylaxis is no longer tenable. The commonly accepted hypothesis is that increased susceptibility is due to the presence of some form of "antibodies," and that intoxication subsequent to anaphylaxis is due essentially to the participation of "antibodies" in forming some toxic substance with the antigen.

It will be necessary to consider as briefly as possible certain of the essential facts that are known concerning anaphylaxis in general, and more especially the anaphylaxis shown by guinea-pigs to horse serum.

Although the reaction of tuberculous animals to the injection

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[*] Received for publication April 6, 1908.

of tuberculin has been known and utilized for diagnosis for a number of years, the proper appreciation of its meaning as an instance of anaphylaxis and of its correlation with similar important though less obvious reactions in animals, was not fully brought out until recently by the work of v. Pirquet, Calmette and others on tuberculosis and on such diseases as small-pox. There is no doubt that a condition of immunity frequently occurs in association with increased susceptibility, but these two conditions of diametrically opposed import to the organism have not been proved to be in any way interdependent. That anaphylaxis is simply a "stage in the development of immunity" is an opinion recently expressed by so high an authority as Richet[2]; but whether this be true, or anaphylaxis be due to a reaction in the body of a nature distinct from the reactions of immunity, as we suspect, the recent studies have at least opened an interesting field of obvious value to our knowledge of the struggle of the organism with disease.

To Otto,[3] and to Rosenau and Anderson[4] working independently, we owe the impetus which has been given to the study of anaphylaxis by the concrete instance which they have demonstrated of the increased susceptibility of guinea-pigs to horse serum, evidenced by the intoxication of these animals on a second administration of serum. These writers found that although normal guinea-pigs support, without symptoms, the injection of any convenient amount of horse serum into the peritoneum, guinea-pigs that have previously been used to test the potency of diphtheria antitoxin (horse serum) or had received a tiny dose of normal horse serum without the addition of the diphtheria toxin present in the toxin-antitoxin mixture would, on a subsequent injection of a relatively large amount of horse serum (five cubic centimeters) into the peritoneum, show severe symptoms of intoxication and frequently die. This reaction of intoxication is, as far as observations extend, present at practically any period of the animal's life subsequent to a necessary period of incubation of about ten days, following the initial dose of serum. It was further shown that animals which had received a large initial dose (four to five cubic centimeters) instead of the usual small dose (.002–.01 cubic centimeter) failed to react after the ordinary incubation period (Otto); and Rosenau and Anderson showed that animals which had received several relatively large, spaced injections (one to two cubic centimeters) showed no symptoms, if injected with a large dose of serum after ten days, and had to all appearances become "immune." The blood of such "immune" animals, however, had no effect in neutralizing the toxic property of horse serum when mixed with it and administered to a sensitive pig. Rosenau and Anderson in particular made a careful study of the effect of various conditions on the toxicity of horse serum, and in addition ruled out certain possibilities such as the formation of precipitates which might have been supposed to cause the intoxication. As a result of their experiments both Otto and Rosenau and Anderson came to similar conclusions as regards the nature of the hypersusceptibility caused by the initial injection, and the intoxication following the second injection. They regard the injection of a small amount of serum as giving rise to "antibodies" which unite with the antigen in horse serum on a second injection and produce a combination toxic to the animal; the injection of a large initial dose or several successive doses would give rise to an immunity, the exact nature of which is not stated. Whether the immunity might depend on the presence of a larger amount of antibodies similar to those which cause the intoxication in the first instance, or on the presence of antibodies of a different nature, is uncertain. At any rate the animal was considered "immune" in the sense that it did not react, although its blood had no power of neutralizing the toxic action of horse serum. In other words, the substance in horse serum which gave rise to the "sensitization" and the substance which intoxicated were identical, as indeed would be essential to explain the intoxication according to the Ehrlich scheme of immunity.

There followed observations by Besredka and Steinhardt,[5] who pointed out that if the toxic dose is injected directly into the brain a much smaller dose will kill; these authors, therefore, were inclined to localize the reaction to some lesion of the brain cells caused by the first injection and intensified by some interaction on the second injection.

Gay and Southard,[1] in their studies on serum anaphylaxis, made several novel observations, as the result of which they came to conclusions regarding the mechanism which are essentially different from the "antibody hypothesis" of the earlier observers. It was found in the first place that the intoxication of guinea-pigs when evidenced by severe symptoms, whether or not followed by death, was almost constantly accompanied by macroscopic lesions in the nature of hemorrhages, which occur in practically any organ of the body, heart muscle, lungs, spleen, and the like, but more particularly in the stomach; microscopically, it was found that these lesions were associated with cellular alterations in the nature of fatty changes, and in some instances, as in the stomach, the fatty changes in the endothelium seemed the cause of the hemorrhages. None of these lesions were noted in a number of "normal" and "sensitized" controls. These authors further demonstrated that the so-called "immune" animals, which had received a single large injection or several spaced injections, eventually become quite as susceptible as do animals which have had a small initial dose, the incubation period varying directly with the amount injected on the first dose or doses. It seemed more correct, then, to refer to these animals as "refractory" rather than "immune." It was further noted that the offspring of such refractory animals, born during a period of full refractoriness in the mother, were not themselves refractory, but sensitive to intoxication by horse serum. It was then determined that normal guinea-pigs which were given small amounts (.1 of a cubic centimeter) of serum from either sensitive or refractory guinea-pigs were themselves sensitive if tested at the end of ten days. This transmitted sensitivity was considered purely an active one, and due to the presence of an unneutralized sensitizing element of horse serum for which the name "anaphylactin" was offered, the function of which was stimulation of the cells of the host which led to an overactive assimilation of, and intoxication by, those other elements of horse serum which had been eliminated in the case of "sensitized" guinea-pigs. The state of refractoriness would be due, then, to the incomplete elimination of the assimilable substances. This conception would assume the existence of two separate substances in horse serum, a sensitizing substance (anaphylactin) which is not assimilable by the guinea-pig tissues, and therefore not easily eliminable, and toxic substances which are assimilated by the guinea-pig tissues. In order to prove that there are these distinct substances in horse serum, recourse was had to injections of "refractory pig" serum directly into the circulation of sensitized guinea-pigs; it was found that although .005 of a cubic centimeter of horse serum injected into the carotid of a sensitive pig will produce symptoms, and .02 of a cubic centimeter will kill; that 1.5 cubic centimeters of refractory pig's serum, which will sensitize normal guinea-pigs in the dose of .1 of a cubic centimeter, produced no toxic symptoms in highly sensitive animals. As the intoxication of sensitive guinea-pigs is evidenced by acute cell lesions in various parts of the body, and the rapidity in the evolution depends on the intimacy and rapidity with which the horse serum comes in contact with the cells, the writers attempted to ascertain whether the intoxication is due to a toxic substance found in the blood stream of the sensitive guinea-pig and then reacting on the cells, or due to a direct action of horse serum on cells "prepared" by the anaphylactin. It was found that mixtures of sensitive guinea-pig serum plus horse serum produced no effect on normal guinea-pigs when injected directly into the circulation, as indeed had been noted by Rosenau and Anderson, and the conclusion was properly drawn that in all probability the reaction of intoxication is located within the body cells, and evidenced, as has been stated, by a rapid fatty change.

It is evident that in this, the most fruitfully studied instance of anaphylaxis, the anaphylaxis of guinea-pigs to horse serum, we have two definite explanatory hypotheses concerning the mechanism of the hypersusceptible condition and its demonstrative intoxication; the hypothesis of Otto, and of Rosenau and Anderson, which may be called the "antibody" hypothesis, and the anaphylactin hypothesis of Gay and Southard, which asserts the existence of two separate components in the active serum, one of which intoxicates and one of which sensitizes. It must be admitted at once that the antibody hypothesis has had practically the united adherence of the workers* on other undoubtedly analogous instances of anaphylaxis, whose opinions, however, are founded mainly on clinical evidence, and in no instance on so well studied an instance of hypersusceptibility as is this serum disease of guinea-pigs.

Since our last publication we have persistently directed our attention toward a further understanding of this horse serum anaphylaxis in guinea-pigs, rather than toward the accumulation of correlative evidence from other forms of hypersusceptibility, and our opinions on these other instances are based largely on literary evidence; our effort has been to gain evidence rather by simplifying known conditions, than by multiplying instances. And in this connection we should like to insist on one point of difference between our work and that of some other observers; with a single exception, which was carefully noted in our first paper, our interpretations have been founded on the intoxication of guinea-pigs sensitized with a uniform anount of *normal horse serum*, and not on animals sensitized with a toxin-antitoxin mixture. It is admitted by Otto[6] and by Lewis,[7] who have both made use, apparently indiscriminately, of animals either sensitized by horse serum alone or by a toxin-antitoxin mixture, that the toxin-antitoxin mixture renders the animal more sensitive than serum alone. While the employment of "used" toxin-antitoxin pigs has the advantage of economy and may, indeed, lead to no erroneous interpretation of results, it is scarcely to be advocated as a clean experimental procedure.

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* No especial reference is here made to those authors whose theories of anaphylaxis agree essentially with our own. With the exception of a review of our article Besredka[24] has not mentioned our work in his publications; several months, however, subsequent to the appearance of our article, he became convinced[25] of the existence of two substances in horse serum, one of which sensitizes (sensibilisogène) and one of which intoxicates (antisensibilisine). He further conceives this "antisensibilisine" as causing intoxication by uniting with a "sensibilisine" of the horse serum and not with the substance which sensitizes. His theory of the mechanism of anaphylaxis although agreeing in part with our own is founded on evidence to us inconclusive. Vaughan and Wheeler have independently determined the presence of two substances in egg white by a method of chemical separation. The work both of Besredka and of Vaughan and Wheeler[31] will be considered more in detail in the following article by Gay and Adler.

Since our consideration of the mechanism of serum anaphylaxis several articles have appeared which contain facts of direct bearing on this phase of the question. Otto,[6] himself still a staunch advocate of the antibody hypothesis, has with great impartiality reviewed and corroborated our work and in addition to further advances in our knowledge of transferred anaphylaxis, has raised certain very logical objections to his own hypothesis. We shall consider first of all these objections to the antibody hypothesis which he admits, before detailing our study on the single objection which he has logically been able to raise against our hypothesis.

The "reaction of fixation" of Bordet and Gengou,[8] which was devised by these writers in their earlier studies on immunity, was used in the first place to prove the presence of specific antibodies against bacteria in the case of certain "antimicrobial" sera which cause no bacteriolysis in vitro. It was later found to be of a clinical diagnostic value even superior to the Widal test in cases of typhoid fever by Lesourd[9] and in cases of cerebrospinal meningitis by Cohen.[10] It depends essentially on the fact that the complex, immune body plus antigen has the power to absorb the alexin (complement) of fresh serum, the absorption or non-absorption of the alexin being proved by the absence or presence of hemolysis in subsequently added, sensitized * blood corpuscles; thus if one of the two factors, antibody or antigen, is known to be present, the existence of the other factor may be determined. The wide applicability of this test has further been shown by its use to prove that a given organism is the cause of a disease, as in the case of the bacillus of whooping-cough, described by Bordet and Gengou,[11] in which case the bacillus (antigen) reacted only

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* That is, corpuscles treated with a specific, inactivated hemolytic serum.

with the blood of children suffering from the disease. The test has been further employed to prove the existence of antigens or antibodies of different nature than bacteriolytic or hemolytic antigens or immune bodies. Thus it has been shown that the interaction of precipitogen and precipitin with or without formation of a visible precipitate also fixes alexin (Gengou,[12] Gay,[13] Moreschi,[14] Neisser and Sachs.[15] *) Very recently Nicolle and Pozerski [16] have shown that the toxins of tetanus and diphtheria, each in presence of its respective antitoxin, will form alexin-fixing combinations. The reaction of fixation has also been asserted to take place in mixtures of cancer emulsion and the serum of cancerous patients by Lüdke.[18] The now generally accepted methods of diagnosis by this reaction introduced in the diagnosis of tuberculosis, syphilis, and general paresis by Wassermann and Bruck,[19] Wassermann and Plaut,[20] and others may be mentioned. The reaction of fixation is, then, the most reliable and delicate diagnostic means of detecting an antibody in the presence of an antigen, or *vice versa*, and, so far as we know, is without exception.

According to Otto the reaction of fixation is lacking in combinations of horse serum and the blood of guinea-pigs sensitive to horse serum. We have also failed to obtain a reaction of fixation, but inasmuch as Otto offers no protocols of his experiments we offer herewith our experimental data with explanation of controls.†

Experiment 1. — On the same day were bled sensitive guinea-pigs No. 40 and No. 11 for ten cubic centimeters each (No. 11 was then given five cubic centimeters of horse serum intraperitoneally and reacted violently). A normal guinea-pig was also bled. The separate sera were heated the next day to 56° C. for thirty minutes. The serum used as "alexin" in the following experiment was from a normal guinea-pig bled three days previously and kept at room temperature. Two identical series of tubes were prepared as follows (numbered 1 to 15; and 16 to 30 respectively):

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* It is of interest to note the most ardent acceptance on the part of adherents of the Ehrlich school, of a method first used by Bordet to prove the unity of the alexin.

† We are aware of the recent assertion of Nicolle and Abt [17] that the reaction of fixation *does* take place between horse serum and the serum of sensitive guinea-pigs, but in the absence of all data from them we unreservedly emphasize the assertions of Otto and ourselves to the contrary.

1.	Serum, sensitive pig No. 40, 56°,	.1	cc.;*	horse serum,	.01	cc.†
2.	“ “ “ “ “ “	.05	“	“ “	.01	“
3.	“ “ “ “ “ “	.02	“	“ “	.01	“
4.	“ “ “ “ “ “	.05	“	“ “	.02	“
5.	“ “ “ “ “ “	.1	“	NaCl	.5	“
6.	NaCl	1.	“	horse serum,	.02	“
7.	Serum, sensitive pig No. 11, 56°,	.1	“	“ “	.01	“
8.	“ “ “ “ “ “	.05	“	“ “	.01	“
9.	“ “ “ “ “ “	.02	“	“ “	.01	“
10.	“ “ “ “ “ “	.05	“	“ “	.02	“
11.	“ “ “ “ “ “	.1	“	NaCl	.5	“
12.	“ normal guinea-pig, 56°,	.1	cc.;	horse serum,	.01	“
13.	“ “ “ “ “	.05	“	“ “	.01	“
14.	“ “ “ “ “	.05	“	“ “	.02	“
15.	“ “ “ “ “	.1	“	NaCl	.05	“

To Series 1 to 15 was then added fresh guinea-pig serum, .05 of a cubic centimeter (diluted in NaCl solution to equal in volume .5 cubic centimeter).

To Series 16 to 30 was added fresh guinea-pig serum, .02 of a cubic centimeter (likewise equal in volume to .5 cubic centimeter). Contact between these mixtures was allowed for five hours at room temperature. To each tube, 1 to 30, was then added .5 of a cubic centimeter of a five per cent suspension of sensitized rabbit's blood (blood previously treated with the inactivated serum of a guinea-pig immunized against rabbit blood [20 cubic centimeters 5 per cent blood + 2 cubic centimeters serum guinea-pig > rabbit No. 3, 56°]).

In Series 1 to 15 the hemolysis of the added blood was complete in all tubes with uniform rapidity within one hour at 37° C In Series 16 to 30 the hemolysis was uniformly marked as "nearly complete" after two hours at 37° C., and the same note was made the next day, after conservation at 0° C. There is, then, in mixtures of the serum of sensitive guinea-pigs ranging from .1 to .02 of a cubic centimeter in amount, and horse serum (.01 or .02 of a cubic centimeter), no evidence of a reaction of fixation even with such doses of alexin as are not sufficient to produce complete hemolysis in the controls.

Another experiment, prepared under similar conditions, but with larger doses of the two sera in question, gave identical results.

Experiment 2. — The preparation of the factors concerned in this experiment is precisely as in the last experiment.

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[*] Made by dilution with NaCl solution (.85 per cent) to equal in all doses one cubic centimeter in volume.

[†] Made by dilution with NaCl solution to equal .5 of a cubic centimeter in volume.

1. Serum, sensitive guinea-pig No. 41, 56°, .5 cc.; horse serum, .05 cc.*
2. " " " " " " " .3 " " " " "
3. " " " " " " " .1 " " " " "
4. " " " " " " " .5 " NaCl .5 "
5. NaCl 1. " horse serum, .05 "
6. Serum, normal guinea-pig 56° .5 " " " " "
7. " " " " " .3 " " " " "
8. " " " " " .1 " " " " "

In the first series (1–8) .05 of a cubic centimeter of guinea-pig alexin was added. In an identical series (9–16) .03 of a cubic centimeter of the same fresh serum was added. After five hours of contact at room temperature, .5 of a cubic centimeter of sensitized five per cent rabbit blood was added, and hemolysis was complete in all tubes within fifteen minutes. The subsequent addition of a second .5 cubic centimeter of the same sensitized corpuscles to the same tubes gave an eventual complete hemolysis in all tubes except 3, 5, and 8 (and corresponding 11, 13, and 16), in which tubes there was little or none; it is of interest to note that these tubes were the ones containing the most salt solution, the presence of which had undoubtedly allowed the more rapid and complete fixation of the free alexin on the first sensitized corpuscles added, leaving little or none for the second corpuscles. The point of importance to us, however, is the fact that there is *absolutely no evidence* of the fixation of the guinea-pig alexin in these mixtures of sensitive guinea-pig serum and horse serum.

Two additional series, each with tubes 1–8, were also made on the same day, and to one of these series was added .05 cubic centimeter of rabbit alexin, and to the other series .075 of the same serum. The resultant hemolysis of sensitized guinea-pig blood (treated with inactivated rabbit > guinea-pig hemolytic serum, and carefully washed to prevent subsequent precipitate formation, and restored to five per cent suspension before adding), showed in each series a *slight inhibition* of alexic activity in the mixtures of *normal* guinea-pigs' serum and horse serum, but no evidence of a reaction of fixation between the sensitive pig serum and horse serum.

By this most delicate reaction method, a method which shows, so far as is known without exception, the presence of antibodies of various natures (antitoxins, immune bodies, both hemolytic and bacteriolytic, and precipitins) no antibodies to horse serum can be demonstrated in the blood of guinea-pigs sensitive to horse serum. Otto has also stated that there is no diminution of alexin in the blood of sensitive guinea-pigs intoxicated by horse serum, which proves in addition that there is no evidence of a reaction of fixation in vivo.

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* Total volumes of each factor the same as in last experiment.

That there is no combination of an antibody and antigen formed by the interaction of the serum of sensitized guinea-pigs and horse serum in vitro, which is toxic, at least for normal guinea-pigs, was shown by the experiments of Rosenau and Anderson, and of ourselves, as already cited. Otto has further stated very briefly that the blood of intoxicated guinea-pigs is not toxic for normal guinea-pigs. This statement, if true, would rule out definitely the formation of a new toxic substance by interaction of antibody and antigen, toxic at least so far as normal guinea-pigs is concerned; that such a substance might be formed and be toxic only for the properly prepared cells of the sensitive guinea-pig is a logical possibility. Let us consider these questions in turn and in detail by the following experiments:

Experiment 3. — A sensitized * guinea-pig was given five cubic centimeters of horse serum intraperitoneally; after severe symptoms for thirty minutes the animal was bled without anesthetic from the carotid and heart; the blood was rapidly defibrinated and kept at approximately body temperature until used. One and one-half cubic centimeters of the defibrinated blood of the above intoxicated pig, a few minutes after taking, was injected into the heart † of a normal guinea-pig (four hundred grams). No serum symptoms.

Experiment 4. — Two sensitive guinea-pigs were injected each with five cubic centimeters of horse serum intraperitoneally. When very sick (fifteen to twenty minutes) they were bled in turn, as in the last experiment, and the blood defibrinated. A normal guinea-pig was bled from the carotid for five cubic centimeters, and four cubic centimeters of the intoxicated, defibrinated blood was carefully injected into the same carotid cephalad. No symptoms, and when the animal was chloroformed an hour later no lesions were found.

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* By sensitized guinea-pig is indicated a normal animal of from 150–300 grams, which has received .01 of a cubic centimeter of horse serum at least two weeks previously. The sensitivity of each lot of pigs was proved by intoxicating one of the animals before using its fellows as "sensitive." Although the sensitivity has been shown not to disappear for several months or years, in the majority of instances it was possible to combine experiments so that a parallel animal could be intoxicated on the very day on which a "sensitive" animal was bled or used as such without intoxication.

† The method of heart inoculation, while in no instance endangering the animal's life, has been abandoned by us after careful trial. In the majority of instances it was found, by killing the animal a few hours after injection, that, although it may have shown no distinctive symptoms of any sort, the pericardium contains a large blood clot. Our experience has been with ordinary hypodermic needles.

Experiment 5. — Two sensitive guinea-pigs were intoxicated as in last experiments, and when symptoms were marked (forty-five and twenty-five minutes respectively) were bled as before. Within a few minutes six cubic centimeters of this blood was injected into the peritoneal cavity of a small (two hundred grams) guinea-pig. No symptoms.

Experiment 6. — Sensitive guinea-pigs Nos. 16 and 18 were given each five cubic centimeters horse serum intraperitoneally and during severe symptoms (fifteen and twenty-five minutes) were bled to death. Blood defibrinated, mixed and kept warm. Normal guinea-pigs received this "intoxicated" blood as follows: No. 49 (five hundred grams) given two cubic centimeters of blood into right jugular; No. 50 given three cubic centimeters of blood into jugular. No symptoms. When chloroformed after five hours no lesions were found in either animal.

Experiment 7. — Sensitive guinea-pigs No. 24 and No. 37 were given each five cubic centimeters of horse serum intraperitoneally. During severe symptoms they were bled (twenty and forty-five minutes). Blood defibrinated and kept warm. A few minutes later normal G.P. No. 62 (about five hundred grams) was bled from left carotid for eight cubic centimeters, and four and one-half cubic centimeters of the mixed defibrinated blood of the intoxicated pigs was injected into the left jugular vein. No symptoms, and, when chloroformed four hours later, no lesions were found.

It is evident from these experiments that the blood of sensitive guinea-pigs intoxicated with horse serum, and bled at different times during symptoms, has no toxicity for normal guinea-pigs, even when injected directly into the circulation in as large amounts as four and one-half cubic centimeters. As we have already mentioned there is the possibility that there might be a combination formed in the blood of the intoxicated animals, which although not toxic for the tissues of normal guinea-pigs, might yet prove so for the properly "prepared" cells of the sensitive animal. The only difference in such an interpretation from our own would be that such an action on the sensitized cells would be indirectly by the horse serum and not directly as we believe to be the case. Such indeed might experimentally seem to be the case from the following experiment were it not for the added control:

Experiment 8. — Under this experiment are collected data obtained at different dates but for simplicity grouped here under one heading. Defibrinated blood was obtained as in the last experiments from sensitive guinea-pigs which had been intoxicated with horse serum, and were undergoing severe symptoms.

Nov. 22, 1907. A sensitive guinea-pig was given one cubic centimeter of intoxicated blood into the heart. Slight symptoms.

Nov. 25, 1907. A sensitive guinea-pig was given one cubic centimeter of intoxicated blood into the heart. Marked symptoms. Recovered.

Dec. 18, 1907. Sensitive guinea-pig No. 15 was given one and one-half cubic centimeter of intoxicated blood into the heart. Slight symptoms.

Sensitive guinea-pig No. 17 was given, of the defibrinated blood of a *normal* guinea-pig, which thirty minutes previous to bleeding had received five cubic centimeters of horse serum intraperitoneally and had shown no symptoms, one cubic centimeter into the heart. *Distinct symptoms* as marked as in No. 15.

It is evident from this experiment that the blood of intoxicated guinea-pigs is indeed toxic for properly sensitized guinea-pigs, but as is shown by the control it is toxic not on account of any new combination of horse serum plus hypothetical "antibody," but on account of *free horse serum* in the blood of the intoxicated animal.

There is, indeed, but a single experiment which has seemed to offer positive evidence for the presence of antibodies to horse serum in the blood of sensitized guinea-pigs. As has been noted we were the first to point out that the injection of normal guinea-pigs with small amounts of the blood of sensitive guinea-pigs leads in two weeks to an active sensitization, as we interpreted it, of the new animal. These results were soon corroborated, and doubtless arrived at independently, by Otto.[6] Lewis[7] later corroborated both our results and also certain additional findings of Otto which are as follows: Otto found that not only will the blood of sensitive guinea-pigs in small amount lead at the end of two weeks to a sensitization of normal animals, but, if given in larger amount, produce sensitization in three days, two days, or even twenty-four hours. This production of sensitivity in a day he very reasonably asserts to be due to a "passive transfer of antibodies," and thinks that our results obtained after the longer interval are due to the same reason. Lewis compromises, and admits that the two-week sensitization, on account of the small amounts employed, is due to a horse serum "rest" (our anaphylactin); he believes, however, that the one-day sensitization is indeed a "passive transfer." In our experiments and in those of Otto and of Lewis the blood was transferred for the most part subcutaneously; this fact would, at first glance, best explain why in Lewis' experiments better results were obtained after two or three days, for, as is known, some such time is necessary for the absorption and distribution of antibodies from the subcutaneous tissue into the circulation. Dehne and Hamburger[21] have shown in man that the absorption of subcutaneously injected antitoxin is never complete in twenty-four hours, but reaches a maximum in from two to three days. J. Henderson Smith[22] has considered this subject even more attentively and determined the time when several different antibodies (agglutinins, antitoxins to tetanus and diphtheria) are to be found in maximal amount in the blood of man, goat or rabbit after subcutaneous injection; his results emphasize the slowness of absorption from the subcutis or even from the peritoneum, and agree as to the height being reached on the third day; he therefore counsels intravenous injections in treatment.

We have been able to corroborate the experiments of Otto and of Lewis as regards the rapid transfer of sensitivity to normal pigs; that this transfer, however, rapid as it is, is no passive transfer of antibodies becomes evident in view of our further experiments. If this transferred sensitivity were indeed due to a passive transfer of antibodies the maximal result with a given amount of transferred blood would, of course, be reached by injection directly into the blood vessels of the normal animal, and results depending on this transfer would be most evident as soon as the circulation had diffused whatever new product had been transferred. It is evident from the following experiment that no such rapid result follows, but *that a period of reaction* is always necessary to produce sensitivity in a normal animal after transfer of blood from a sensitive animal directly into the circulation.

Experiment 9. — Sensitive guinea-pigs No. 25 and No. 39 were bled from the carotid and the blood defibrinated.

Normal guinea-pigs Nos. 62, 63, 64 (weights about four hundred grams) were then in turn bled for approximately five cubic centimeters from the carotid, and there then was injected slowly into the jugular of the same side five cubic centimeters of the defibrinated blood of the above sensitive animals. (This operation is found to present no great difficulties if the animal is previously bled so as to reduce the blood pressure, and the cannula needle inserted into the vein is small and connected with the syringe by means of a flexible rubber tube. An assistant is necessary.) These three animals showed no marked effect from the operation and were given seven cubic centimeters of horse serum into the peritoneal cavity at the following times: No. 63, three hours after receiving sensitive blood; no symptoms. No. 62, three days after receiving sensitive blood; marked symptoms. No. 64, six days after receiving sensitive blood; marked symptoms.

Let us accept for the moment the fact, evidenced by this single experiment, that the rapidly transferred anaphylaxis requires a definite period of incubation or reaction. It is evident, then, that we have to deal with no passive transfer of antibodies, else the reaction would be most marked directly after transfer into the circulation. It is certain that the tissues of the animal must in some way react to the injected blood, containing the unneutralized anaphylactin of horse serum which (although it produces as we have shown a more complete sensitization at the end of two weeks) has already produced some sensitivity within twenty-four hours. In other words, this one-day transferred sensitivity is only a lesser state of our two-week transferred sensitivity. That a foreign substance (anaphylactin) may increase the assimilating property of the cell, which is the gist of our theory, and in the same short space of time as in the above experiments, is very neatly proved by the closely analogous instance recently described by Calmette, Breton and Petit.[23] These authors have shown that if a normal rabbit be given tuberculin intravenously it will give the typical ophthalmo-reaction to tuberculin after sixteen hours.

That the rapid transfer reaction of Otto is identical with the transferred anaphylaxis of Gay and Southard, but evidenced after a shorter interval than we had deemed probable, and that this reaction is simply an evidence of active sensitization on the part of our anaphylactin, is rendered certain by the following experiments. It will be remembered that we noted in the case of our transfer experiments that the sensitivity in the inoculated animals tested at the end of two weeks was much more evident with a given dose of "refractory" pig serum than with the same amount of sensitive pig serum; it will further be remembered that a refractory pig is one which has received at first much more horse serum than the sensitive pig and obviously by this process has retained more anaphylactin; that such an animal will react to horse serum only after a long period of incubation we explained by the necessity of a longer time to eliminate from the cells the assimilable elements of horse serum injected in the large initial dose or doses. It may be shown experimentally that the short-period transferred sensitivity likewise succeeds better if refractory pig blood is used, but that here also a distinct reaction period is necessary even after intravenous injection.

Experiment 10. — Refractory guinea-pig No. 3 * was bled to death and the blood defibrinated.

Normal guinea-pigs were treated as follows:

G.P. No. 45. Given 4.5 cubic centimeters refractory pig's blood, into the jugular.

G.P. No. 47. Given 4.5 cubic centimeters of blood of refractory pig blood intraperitoneally.

G.P. No. 46. Given 4.5 cubic centimeters refractory pig blood intraperitoneally.

Subsequent treatment: G.P. No. 45. Forty minutes after injection given .05 of a cubic centimeter of horse serum into the heart. No symptoms. (This animal was killed four days later and showed no lesions except a healed scar in left auricle No evidence of hemorrhage into pericardium.)

G P. No. 47. Twenty-four hours after injection, given 05 of a cubic centimeter of horse serum into the heart and fifteen minutes later five cubic centimeters of horse serum intraperitoneally. Distinct paralytic symptoms. Recovered.

G.P. No. 46. Five days after injection given five cubic centimeters of horse serum intraperitoneally. Severest prostrating symptoms. Recovered.

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* In each instance where a pig was used as "refractory" another pig previously treated in the same manner was given horse serum and shown not to react.

In this experiment on account of slight differences of treatment only pigs No. 47 and No. 46 may strictly be compared. The increased sensitization of five days over one day is marked in these two animals, however.

Experiment 11. — Refractory guinea-pigs No. 34 and No. 35 were bled and the blood defibrinated, mixed, and kept warm. Normal guinea-pigs were treated as follows:

G.P. Nos. 52, 53, 54. Given each three cubic centimeters of refractory blood into the left jugular.

G.P. No. 55. Given three cubic centimeters refractory pig blood subcutaneously.

Subsequent treatment: G.P. No. 52. Three hours after injection given five cubic centimeters of horse serum intraperitoneally. No symptoms. Chloroformed after eighteen hours; no lesions.

G.P. No. 53. Twenty-two hours after injection given five cubic centimeters of horse serum intraperitoneally. No symptoms.

G.P. No. 54 and No. 55. Three days after injection given each five cubic centimeters of horse serum intraperitoneally. No. 54 (jugular) showed severe, and No. 55 (subcutaneous), distinct symptoms.

This experiment would indicate by comparison with experiment No. 9 that refractory pig's blood sensitizes better in the short interval than does sensitive pig's blood; and also that the subcutaneous injection of refractory pig's blood is less quickly sensitizing than the intravenous.

To demonstrate conclusively the relatively higher sensitizing power of refractory pig's blood over sensitized pig's blood the following experiments are added in tabulated form:

Experiment 12. — Normal guinea-pigs received subcutaneously the amounts of sensitive or refractory pigs' defibrinated blood noted; and on the third day were given five cubic centimeters of horse serum intraperitoneally.

Pig No.	Treatment.	Symptoms on Inoculation of Horse Serum Three Days Later.
33	3.5 cubic centimeters sensitive blood.	Distinct, but moderate.
34	3.5 cubic centimeters sensitive blood and twenty-four hours later 3.5 cubic centimeters sensitive blood.	Distinct, but moderate.
35	3.5 cubic centimeters refractory pig's blood.	Severe symptoms.

Experiment 13. — Normal guinea-pigs received of sensitive or refractory pigs' blood subcutaneously, the amount indicated in the table, and, after three days, were each given five cubic centimeters of horse serum intraperitoneally.

Pig No.	Treatment.	Symptoms on Injection of Horse Serum.
56.....	4 cubic centimeters sensitive blood.	Very severe. Recovered.
57.....	2 cubic centimeters sensitive blood.	Distinct.
58.....	1 cubic centimeter sensitive blood.	No symptoms.
59.....	4 cubic centimeters refractory blood.	Severe. Recovered.
60.....	2* cubic centimeters refractory blood.	Slight, if any.
61.....	1 cubic centimeter refractory blood.	*Marked.*

A comparison of the symptoms in pigs No. 58 and No. 61 is particularly to be noted.

Still clinging to the logical possibilities of the antibody hypothesis, which in the face of the evidence we have presented can scarcely be further maintained, it might be well to inquire how the rapid sensitization of normal animals by the blood of refractory animals can at all be accounted for. In the instance of the longer period transferred anaphylaxis, if one admits this to be an instance of active sensitization, it is evident that the refractory pig's blood would contain more anaphylactin than does the blood of sensitive pigs, and so transfer better. Might it still be possible to explain the superior rapid transferring power of refractory pig's blood on the antibody hypothesis, admitting for the moment that other evidence supported this hypothesis? These refractory pigs, as we have defined them, are always bled at least two weeks after the last injection, in other words they are bled at a period favorable for such antibodies as are formed, and, as we have shown, precipitins to horse serum are often present; if these refractory animals possess antibodies to which anaphylactic intoxication might be due they certainly possess them in a greater amount than do the sensitive pigs. Since refractory guinea-pigs are temporarily non-reactive to horse serum but become so later on, this condition, on an antibody hypothesis, might be explained as an excess of antibodies, and the sensitive condition as due to an optimal minimum of the same antibodies. If this were the true explanation the bleeding of refractory pigs, thus removing mechanically some of the antibodies, might cause them to become sensitive at an earlier period. Experiment shows, however, that no such effect occurs.

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* In this animal at least one-half the blood escaped after injection.

Experiment 14. — Four sensitive guinea-pigs had been used for another experiment and on receiving five cubic centimeters of horse serum on the same day had reacted with more or less symptoms. Eleven days later one of them was given five cubic centimeters of horse serum intraperitoneally and showed no symptoms; another one was bled from the carotid, on the same day, for six and one-half cubic centimeters, and one hour later also given horse serum in the same manner and amount and showed no symptoms. On the sixteenth day a similar pair bled and unbled were given horse serum; both showed distinctive symptoms, the unbled animal reacting more violently than the bled one.

There seems, then, no reason to believe that the change of a refractory to sensitive state is due to the lowering of antibody content to a certain optimal minimum.

Certain of our experiments on the bleeding of sensitive animals offer strong presumptive evidence that the intoxication by horse serum is in no way due to the presence of hypothetical antibodies in the blood of the sensitive animals. If there were any such substances in the blood of sensitive animals we should expect that the abstraction of a relatively large amount of blood from them at least to reduce the severity of the symptoms on subsequent injection of horse serum. In the following experiment are grouped the results of such treatment on several sensitive animals performed at different times.

Experiment 15. — 1. Sensitive guinea-pig No. 26 was bled on February 1 for six cubic centimeters from the carotid. Given five cubic centimeters of horse serum on February 25 intraperitoneally. Severe symptoms. Recovered.

2. Sensitive guinea-pig No. 29 was bled for ten cubic centimeters from the carotid on February 27, and on March 10 given five cubic centimeters of horse serum intraperitoneally. Very severe symptoms.

In these two animals the question may be properly raised as to a possible regeneration of antibodies after bleeding. The evidence for such a regeneration is still in doubt; the results of Friedberger and Dorner [27] would seem to show that a severe bleeding leads to the diminution of antibodies. In the following animals no such objection can be raised since the animals were intoxicated soon after bleeding:

3. Sensitive guinea-pig No. 11 was bled on March 5, from the carotid for ten cubic centimeters, and one hour later given six cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.

4. Sensitive guinea-pig No. 27 was bled on February 27 for eight cubic centimeters and on March 13 for eight additional cubic centimeters; thirty minutes later was given five cubic centimeters of horse serum intraperitoneally. Very extreme symptoms and died in one hour. Hemorrhages cecum, kidney and lungs.

5. Sensitive guinea-pig No. 43, weight three hundred and ninety grams, was bled as much as possible from one carotid (12.5 cubic centimeters) and then given six cubic centimeters of the defibrinated warmed blood of a normal pig into the other carotid; and six cubic centimeters of NaCl solution into the peritoneal cavity. Rapid recovery. After sixteen hours the animal was given five cubic centimeters of horse serum intraperitoneally. Dead one hour; hemorrhages of lungs and stomach.

For the sake of completeness there may be mentioned at this point the result of a chemical study of horse serum by Gay and Adler, a full consideration of which is detailed in the following article. This study, although not ended, has shown that by means of fractional precipitation with ammonium sulphate a substance may be obtained (one-third saturation or euglobulins) which possess all the characteristics of a pure sensitizing substance without admixture of any of the toxic or assimilable elements. So far a relatively pure toxic substance has not been obtained.

DISCUSSION.

The theory of anaphylaxis which we offered a year ago as explanatory of the hypersusceptibility and intoxication of guinea-pigs brought about by horse serum, seems to us by the additional evidence from the continued study of this instance of anaphylaxis, and the literary evidence from other analogous instances, not only uncontroverted but more fully than ever justified. Increased susceptibility in the sensitized animal is due to the continued presence in the circulation of an unneutralized element of horse serum (anaphylactin) which acts as an irritant or stimulant to the body cells and in some way causes them to assimilate over rapidly certain other elements of horse serum. These assimilated or toxic elements are the same as those eliminated, without producing intoxication, during the incubation period following the first dose. This over-assimilation after anaphylaxis is the cause of the intoxication. This conception, although novel as applied to anaphylaxis, has, nevertheless, certain analogies. The "chemical messengers" or specific stimulating substances described by Bayliss and Starling[28] as "hormones" have many points in common with our anaphylactin. It has also been shown by Reid Hunt[29] that a well-known chemical substance, alcohol, will so stimulate the assimilating power of the body cells that the subsequent injection of acetonitrile, in doses harmless to a normal guinea-pig, will, in alcoholized animals, lead to so rapid an oxidation or cleavage of this product that the animal is poisoned; the striking analogy of this form of intoxication, involving as it does the intervention of two definite chemical substances, to the serum disease of guinea-pigs, is evident in the light of our hypothesis.

We were led to assume the existence of an unneutralized substance in horse serum (anaphylactin) which causes the sensitivity in treated guinea-pigs, because we found not only that the blood of sensitive animals, but still more so the blood of refractory animals would transmit sensitivity to normal guinea-pigs. Not only may this transmitted sensitivity be demonstrated two weeks after transfer, as we were first to show, but, if the doses are sufficient, it may be shown in a single day (Otto). That the substance in the blood of sensitive animals which causes sensitivity and transmits it to normal animals is not an antibody to horse serum, but some retained substance of horse serum is evident for the following reasons:

First, it is a characteristic of antibodies that they disappear rapidly from the blood unless the antigen is reinjected, and the sensitivity of guinea-pigs after a single minute injection of horse serum is present for months or years.

Second, the serum of sensitive guinea-pigs gives no "reaction of fixation" with horse serum. This reaction detects the presence of the smallest amounts of antibodies of various known varieties, and, so far as is known, without exception.

Third, although sensitivity may be transmitted in a day or so by the transfer of blood from a sensitive or refractory to a normal animal, this second animal, even when injected directly into the circulation, requires a distinct reaction period before becoming in turn sensitive.

Fourth, this rapidly produced sensitivity may be given to normal animals by the injection of a chemically separated fraction of horse serum (euglobulins), whereas whole horse serum in the optimum dose requires the ten-day incubation period. A similar rapid anaphylaxis is said to occur after the injection of tuberculin in rabbits (Calmette, Breton and Petit).

Fifth, the superior sensitizing power of a toxin-antitoxin mixture over normal horse serum, generally admitted and still further emphasized by a comparison of our present results with those of Otto or Lewis, cannot be accounted for on the ground of more antibodies to horse serum.

Sixth, the blood of refractory animals which temporarily are non-reactive, but which have received more horse serum than simply sensitized animals, transmits sensitivity better than the blood of these latter animals. This refractory condition, however, cannot be accounted for as due to an excess of "anaphylactic reaction bodies" for bleeding, and so mechanically abstracting such bodies, were they present, does not cause refractory animals to become sensitive.

That the intoxication of sensitive animals by horse serum is not due to a toxic substance, formed of an antibody plus antigen, and that moreover the reaction of intoxication takes place, not in the circulation of the animal but in the prepared cells, is evident because:

First, neither the blood of sensitive animals mixed with horse serum, nor the blood of animals undergoing intoxication is toxic for normal guinea-pigs when injected directly into the circulation. The blood of intoxicated animals is somewhat toxic for a sensitive animal, but owing solely to the presence of free horse serum in the blood.

Second, the abstraction of relatively large amounts of blood from sensitive animals (such as 12.5 cubic centimeters), whether or not followed by transfusion of normal blood, does not cause these animals to become less sensitive.

Third, acute cellular lesions in the nature of a fatty change occur regularly in sensitive animals on intoxication with horse serum. The localization of these lesions depends on the point of access of the serum to the circulation, and the rapidity with which these lesions may be formed depends on the rapidity with which the horse serum comes in contact with the cells. Two or three minutes at most will suffice under favorable conditions.

It is clear, then, that the sensitivity of guinea-pigs to horse serum is associated with the persistence of an unneutralized element of horse serum in the sensitive animal, and that the intoxication is due to some condition of the body cells which renders them particularly susceptible to those elements of horse serum that have been already eliminated from the first dose. The prepared condition of these cells might lead some to associate their sensitive condition with the "sessile receptors" of Ehrlich, and it is, therefore, well to point out that no such analogy exists. In the first place this sensitive cell condition depends entirely on the presence of an unneutralizable element, anaphylactin, which, by our definition, finds no "receptor" in the cell, and secondly, the entire "receptor hypothesis," as has recently been shown by Bang and Forsmann[26] and Landsteiner,[30] can be proved experimentally to be without foundation, as an explanation of reaction products. Bang and Forsmann have shown that the substance in blood which stimulates the formation of hemolytic antibodies in animals of another species, is chemically separable from the substance in blood which unites with these antibodies; the "receptors" or cell affinities, therefore, are not identical with the antibodies. It is evident simply that the cells of animals sensitive to horse serum have an increased assimilating, oxidizing, or cleaving power, which, when the serum is presented to such cells, is manifested by an over-activity indicated by the occurrence of fat. It would be purely speculative to consider the basis of the functional change in the cell which leads to this over-assimilating power, but we are by no means convinced that such changes may not some day be morphologically demonstrated.

BIBLIOGRAPHY.

1. Gay and Southard. On serum anaphylaxis in the guinea-pig. Jour. of Med. Research, xvi, 1907, 143.

2. Richet. De l'anaphylaxie en général et de l'anaphylaxie par mytilo-congestine en particulier. Annales de l'Institut Pasteur, xxi, 1907, 497

3. Otto. Das Theobald Smithsche Phaenomen der Serum-Über empfindlichkeit. Leuthold Gedenkschrift, Berlin, 1906

4. Rosenau and Anderson. A study of the cause of sudden death following the injection of horse serum. Bull. No. 29, Hyg. Lab., U.S. Pub. Health and Mar. Hosp. Serv., Washington.

5. Besredka and Steinhardt. De l'anaphylaxie at de l'antianaphylaxie vis à vis du serum de cheval. Annales de l'Institut Pasteur, xxi, 1907, 117.

6. Otto. Zur Frage der Serum-Ueberempfindlichkeit. Münch. Med. Wochensch., No. 34, 1907.

7. Lewis. The induced susceptibility of the guinea-pig to the toxic action of the blood serum of the horse. Jour. Exper. Medicine, x, 1908, 1.

8. Bordet and Gengou. Sur l'existence de substances sensibilisatrices dans la plupart des sérums antimicrobiens. Annales de l'Institut Pasteur, xv, 1901, 289.

9. Lesourd. Recherches expérimentales et cliniques sur la présence d'une sensibilisatrice spécifique dans le sérum des typhiques. Thèse de Paris, 1902.

10. Cohen. Sur les propriétés sensibilisatrices du sérum d'un enfant convalescent de méningite cerebro-spinale. Bull. de la Soc. Roy. de Sc Méd. et Nat de Bruxelles, 1906, 158.

11. Bordet and Gengou. Le microbe de la Coqueluche. Annales de l'Institut Pasteur, xx, 1906, 731.

12. Gengou. Sur les sensibilisatrices des sérums actifs contre les substances albuminoides. Annales de l'Institut Pasteur, xvi, 1902, 734.

13. Gay. The fixation of alexines by specific serum precipitates. Cent. für Bakt., 1 Abt. Orig., xxxix, 1905, 603. La déviation de l'alexine dans l'hémolyse. Annales de l'Institut Pasteur, xix, 1905, 593.

14. Moreschi. Zur Lehre von den Anti-Komplementen. Berl. Klin. Wochensch., 1905, 1181.

15. Neisser and Sachs. Ein Verfahren zum forensischen Nachweiss der Herkunft des Blutes. Berlin. Klin. Wochensch., 1905, No. 44.

16. Nicolle and Pozerski. Une conception générale des anticorps et de leurs effets. Annales de l'Institut Pasteur, xxii, 1908, 26.

17. Nicolle and Abt. Une conception générale des anticorps et de leurs effets. Annales de l'Institut Pasteur, xxii, 1908, 132.

18. Lüdke. Zur Kentniss der Komplemente. Verhand. der physical. medicin. Gessell. Wurtzburg, xxxix, 1908, No. 3.

19. Wassermann and Bruck. Experimentelle Studien uber die Wirkung von Tuberkelbacillen-Präparaten auf den tuberculos Organisms. Deutsch. Med. Woch., 1906, 448.

20. Wassermann and Plaut. Ueber das Vorhandsein syphilitisches Antistoffe in der Cerebrospinalflüssigkeit. Deutsche. med. Woch., 1906, 1769.

21. Dehne and Hamburger. Ueber das Verhalten artfremden Antitoxins in menschlichen Organisms. Wien. Klin. Wochen., xx, 1907, 817.

22. J. Henderson Smith. On the absorption of antibodies from the subcutaneous tissues and peritoneal cavity. Jour. of Hygiene, vii, 1907, 205.

23. Calmette, Breton and Petit. Etude expérimentale de l'opthalmoreaction à la Tuberculine. Comptes rend. de la Soc. de Biol., lxiii, 1907, 296.

24. Besredka. Bulletin de l'Institut Pasteur, v, 1907, 850.

25. Besredka. Du mechanisme de l'anaphylaxie vis à vis du sérum de cheval. Comptes rend. de la Soc. de Biol., lxiii, 1907, 295.

26. Bang and Forsmann. Untersuchungen über Hämolysinbildung. Beträge z. Chem. Physiol. und Pathol., viii, 1906, 238.

27. Friedberger and Dorner. Ueber Hämolysinbildung durch Injektion kleinster Mengen von Blutkörperchen und über den Einfluss des Aderlasses auf die Intensität der Bildung hämolytischer Ambozeptoren beim Kaninchen. Cent. für Bakt., xxxviii, 1905, 544.

28. Starling. The chemical control of the body. Jour. Am. Med. Ass., l, 1908, 835.

29. Hunt. Studies in experimental alcoholism. Bull. No. 33, Hyg. Lab., U.S. Pub. Health and Mar. Hosp. Serv., Washington.

30. Landsteiner and Reich. Ueber den Immunisierungsprozess. Zeit. für Hyg., lviii, 1907, 213.

31. Vaughan and Wheeler. The effects of egg-white and its split products on animals. Jour. of Infect. Diseases, iv, 1907, 476.

FURTHER STUDIES IN ANAPHYLAXIS.*

II. *On Recurrent Anaphylaxis and Repeated Intoxication in Guinea-pigs by Means of Horse Serum.*

F. P. GAY AND E. E. SOUTHARD.

(*From the Pathological Laboratories of the Harvard Medical School and the Danvers Insane Hospital.*)

In a previous article[1] (1907) we have shown that the stage of "immunity" (Rosenau and Anderson, and Otto) or "anti-anaphylaxis" (Besredka and Steinhardt) which follows several moderate-sized injections or one large initial injection without intoxication, or which is present in animals after the intoxication caused by a second spaced dose of horse serum, is in reality not a state of immunity, properly speaking, but a refractory condition. The animals in this refractory condition contain no elements in their blood capable of neutralizing the toxic effect of horse serum, although their blood does contain, at times, other reaction bodies, such as precipitins. So far as they themselves are concerned as regards intoxication by horse serum, they are essentially in a condition similar to guinea-pigs which have just received a small initial dose of serum, for they eventually become sensitive to the toxic action of this serum; they differ from guinea-pigs sensitized by the small dose only in undergoing a longer period of incubation. The fact that animals who had received a single large initial dose, or several doses, showed an incubation period proportionate to the amount of serum injected was of importance in the evolution of our hypothesis, which insists on the

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presence of two substances in horse serum: the unassimilable anaphylactin which sensitizes and the assimilable elements which are gradually eliminated, and the subsequent ingress of which to properly prepared cells give rise to the intoxication. It is the presence of a large amount of assimilable substances, which naturally require time for their elimination, that, in the case of the large initial dosage, requires a longer period of incubation. A condition in the refractory animal of complete or nearly complete assimilation but of little or beginning elimination of the toxic element would account for the nonreaction of these animals to horse serum and explain why, at the same time, their blood on transference is more sensitizing for normal guinea-pigs than is the blood of sensitive guinea-pigs — since they have obviously much more of the anaphylactin, but little or none of the toxic substance of horse serum remaining unassimilated.

The point which we wish to emphasize in the present section is not that animals receiving a large dose of serum eventually become sensitive, but the fact that a sensitive animal intoxicated with a large dose, and recovering and thereby passing into a refractory state (antianaphylaxis of Besredka and Steinhardt), by the same mechanism again becomes sensitive to the toxic effect of horse serum. This fact has indeed already been evidenced in our own protocols and in those of other workers. We previously stated — "As may have been deduced from our observation of the refractory guinea-pigs and their eventual sensitivity, animals which have once suffered severe symptoms and recovered, if reinjected after a sufficient period, may be made to undergo again the typical serum intoxication. By a proper dosage the disease may be repeated at relatively short intervals and as frequently as desired."

It might be possible to draw an analogy between this form of recurrent hypersusceptibility, due indirectly to an intoxication, and the evidence of repeated intoxication in some diseases characterized by "crises" or repeated attacks, such as general paresis, epilepsy, and purpura, the only point of analogy which would be difficult to explain being the reintoxication — which in this experimental disease of guinea-pigs is artificially induced. It is of advantage, however, to present concretely the protocols of certain animals that for the purpose of histological study have been intoxicated with serum two or three times.

I. Guinea-pigs showing secondary intoxication:

G.P. No. 46.	Jan. 2, 1907.	Given three cubic centimeters of horse serum subcutaneously.
	Jan. 17, 1907.	Given five cubic centimeters horse serum intraperitoneally. Slight symptoms. Recovered.
	April 9, 1907.	Given three cubic centimeters of horse serum intraperitoneally. Dead sixty minutes. Gastric and pulmonary hemorrhages.
G.P. No. 50.	Jan. 9, 1907.	Given 1.5 cubic centimeters serum of refractory guinea-pig "B."
	Jan. 24, 1907.	Five cubic centimeters horse serum intraperitoneally. Severe symptoms. Recovered.
	April 25, 1907.	Two cubic centimeters horse serum intraperitoneally. Dead in twenty minutes. Hemorrhages of heart, lungs, and stomach.
G.P. No. 47.	Jan. 2, 1907.	Given .01 of a cubic centimeter of horse serum subcutaneously.
	Jan. 17, 1907.	Five cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.
	April 9, 1907.	Three cubic centimeters of horse serum intraperitoneally. Dead one hour. Hemorrhages of lungs.

II. Guinea-pigs showing tertiary intoxication:

G.P. No. 37.	Dec. 24, 1906.	Given .01 of a cubic centimeter of horse serum.
	Jan. 10, 1907.	Given five cubic centimeters of horse serum intraperitoneally. Severe symptoms. Recovered.
	March 28, 1907.	Given one cubic centimeter of horse serum intraperitoneally. Slight symptoms.

G.P. No. 37.	April 25, 1907.	Given seven cubic centimeters of horse serum intraperitoneally. Distinct but moderate symptoms. Chloroformed four hours. Gastric and pulmonary hemorrhages.
G.P. No. 30.	Dec. 26, 1906.	Given .01 centimeter of horse serum subcutaneously.
	Jan. 8, 1907.	Given five cubic centimeters horse serum intraperitoneally. Severe symptoms. Recovered.
	March 28, 1907.	Given one cubic centimeter horse serum intraperitoneally. Slight symptoms. Recovered.
	April 25, 1907.	Given ten cubic centimeters horse serum intraperitoneally. Severe symptoms. Chloroformed four hours. Hemorrhages of stomach, lungs, kidney, liver.

BIBLIOGRAPHY.

1. Gay and Southard. On serum anaphylaxis in the guinea-pig. Jour. Med. Research, xvi, 1907, 143.

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FURTHER STUDIES IN ANAPHYLAXIS.*

III. *The Relative Specificity of Anaphylaxis.*

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Rosenau and Anderson,[1] in their first article on the anaphylaxis in guinea-pigs produced by horse serum, considered the relative specificity of the reaction. They found that guinea-pigs which had been sensitized by a small dose of horse serum could be intoxicated after an interval of ten days by a subsequent dose not only of horse serum, but also to a less extent by serum from other animals; conversely, animals sensitized by other sera became more or less susceptible to horse serum. In each combination, however, a relative ("quantitative") specificity was to be noted, for in each instance the maximum reaction was obtained if the serum used for first and second injections was the same. These authors later[2] apparently showed that when protein substances of a more divergent origin are used the specificity becomes more apparent. Thus they showed that such substances as egg white, milk, and extract of peas, when given to guinea-pigs in successive spaced doses will cause intoxication on the second dose. According to the protocols of Rosenau and Anderson these different instances of anaphylaxis showed absolute specificity; that is, sensitization by milk, egg white, or horse serum was followed by intoxication only when the same substance which had sensitized was used for a second dose.

In a recent and most interesting article,[3] the same writers have continued their observations on this subject of the specificity of anaphylaxis. They have shown that if guinea-pigs be given a mixture of horse serum, egg white, and milk they become, after the proper period of incubation, susceptible to intoxication by each of these substances in turn, when

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administered on following days or even on the same day. It is well known that if a guinea-pig sensitive to horse serum recovers from a second dose of the serum, it immediately passes into a refractory stage and is unaffected by another dose of horse serum, for at least several weeks. This fact renders still more striking this serial intoxication with different substances after mixed sensitization with the same substances, and makes it seem that each reaction is, indeed, absolutely specific.

We have recently considered this question of the specificity of anaphylaxis, and our results, although agreeing in the main with those of Rosenau and Anderson, differ in essential particulars. In our hands the matter of specificity has been proved to be by no means absolute. It is clearly shown in the tables that follow that although an animal sensitized by a given proteid will react most violently to a second injection of the same proteid, it will frequently show distinct intoxication on injection of a proteid of different origin.

TABLE I.

These animals were given each one cubic centimeter of egg white (1 egg to 10 cc. NaCl sol.) subcutaneously as a first injection and at a subsequent injection were given the substances noted below.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
154.....	16 days.	4 cc. egg white subcutaneously.	Moderate.
151.....	16 days.	5 cc. egg white intraperitoneally.	Dead 10 minutes.
112.....	35 days.	5 cc. egg white intraperitoneally.	Dead 20 minutes.
152....	16 days.	4 cc. horse serum subcutaneously.	Slight.
150.....	16 days.	10 cc. horse serum intraperitoneally.	Severe.
113.....	35 days.	5 cc. horse serum intraperitoneally.	Dead 1 hour.
153.....	16 days.	4 cc. milk subcutaneously.	Suggestive.
149.....	16 days.	10 cc. milk intraperitoneally.	Doubtful.
114.....	35 days.	5 cc. milk intraperitoneally.	Distinct.

From Table 1 it appears that guinea-pigs sensitized with egg white react not only to egg white but very markedly to horse serum and less distinctly to milk. Under more favorable conditions, such as a longer period before intoxication, it seems indicated that the reaction to milk would be more notable.

TABLE 2.

These animals were sensitized with one cubic centimeter of whole milk subcutaneously.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
80......	13 days.	5 cc. milk subcutaneously.	Distinct.
107.....	35 days.	6 cc. milk intraperitoneally.	Very severe.
81......	13 days.	5 cc. horse serum subcutaneously.	Marked.
110.....	35 days.	6 cc. horse serum intraperitoneally.	Very severe.
155.....	16 days.	10 cc. egg albumin intraperitoneally.	Doubtful symptoms.
108.....	35 days.	5 cc. egg albumin intraperitoneally.	Slight.

From Table 2 it is evident that guinea-pigs sensitized to milk will react on second injection not only to milk but quite as distinctly to horse serum; the reaction to egg white after milk is only slight.

TABLE 3 *a*.

These animals had received .01 of a cubic centimeter of horse serum subcutaneously as a first injection.

G. P. No.	Interval.	Second Injection.	Resulting Symptoms.
106	35 days.	5 cc. egg albumin.	Distinct but slight symptoms.
104	35 days.	5 cc. milk.	Doubtful symptoms.

TABLE 3 *b*.

These animals had received five cubic centimeters of horse serum subcutaneously as a first injection.

G.P. No.	Interval.	Second Injection.	Resulting Symptoms.
24	44 days.	7 cc. egg albumin intraperitoneally.	No symptoms.
48	28 days.	8 cc. egg albumin intraperitoneally.	No symptoms.
26	41 days.	7 cc. egg albumin intraperitoneally.	Doubtful.
29	28 days.	6 cc. milk intraperitoneally.	No symptoms.

Only the slightest indication of symptoms can be elicited by egg albumin or milk after sensitization by horse serum in the doses used. It is probable that, although under the conditions of sensitivity here given the animals are known to be highly sensitive to horse serum, the intoxication by the other proteids, which is only suggested, might be made more clear by a longer anaphylactic period or different initial dose.

A study of these tables shows that animals sensitized with either egg white or milk will react more or less characteristically to horse serum. It may also be seen that after sensitization with egg white guinea-pigs will react faintly to milk; and after sensitization with milk will react slightly to egg white. The reaction to egg white after sensitization with horse serum was noted as distinct in only one instance; the reaction to milk after horse serum was not to be noted in one instance and was doubtful in the other.*

A comparison of these different tables indicates in the first place that anaphylaxis is only relatively specific; and the fact that, in certain combinations (*e.g.*, sensitization with horse serum followed by milk or egg), an absolute specificity would seem to be present leads to correlative conclusions of interest. It is obvious that after sensitization by a given substance the maximum intoxication is caused by the same substance; we might refer to this as the "complete" intoxication; in addition there may or may not be "partial" intoxication by the other protein substances. It has been shown by our previous studies[4] that in the case of horse serum anaphylaxis, the substance of the serum which sensitizes (anaphylactin) is not identical with the substance which intoxicates. The distinction in these substances is brought out more clearly when we consider these instances of "crossed" intoxication. Horse serum has little or no power to sensitize against the other two proteids, while milk and egg have a more "general" anaphylactizing power; on the other hand, horse serum intoxicates readily after sensitization with one of the other substances, egg less readily, and milk still less so.

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*Since our results apparently refute the observations of Rosenau and Anderson on the specificity of these reactions we have accepted them only after repeated corroboration. As is indicated in the tables the animals tested for cross intoxication were put through in several separate lots. It is perhaps not gratuitous, in view of the small amount of horse serum which will produce anaphylaxis, to insist that the animals used not only had never themselves been previously used, but were the offspring of normal animals; the syringes used for the sensitizing dose, although they had been repeatedly washed, were boiled for from fifteen to twenty minutes before using.

When we consider the serial intoxication by the different proteids after sensitization by a single substance, either milk or egg, the relation of a "partial" to a "complete" intoxication is brought out more clearly.

TABLE 4.

These guinea-pigs had been sensitized by previous injection of one cubic centimeter of egg white sixteen days previously.

G.P. No.	Date.	Given	Result.
153	March 20, 1908.	4 cc. milk subcutaneously.	Suggestive symptoms.
	March 21, 1908.	5 cc. horse serum intraperitoneally.	Marked symptoms.
	March 23, 1908.	5 cc. egg albumin intraperitoneally.	Marked symptoms.
150	March 20, 1908.	10 cc. horse serum intraperitoneally.	Severe symptoms.
	March 21, 1908.	5 cc. egg albumin.	Severe symptoms.
152	March 20, 1908.	4 cc. horse serum subcutaneously.	Slight symptoms.
	March 21, 1908.	5 cc. egg albumin intraperitoneally.	Dead 30 minutes.
154	March 20, 1908.	4 cc. egg albumin subcutaneously.	Moderate symptoms.
	March 21, 1908.	5 cc. horse serum intraperitoneally.	No symptoms.

This table shows that even after "partial" intoxication has been caused in animals sensitive to egg white, by one or even by both of the other proteids in turn (G.P. No. 153) a succeeding set of symptoms may be elicited by egg white. When, however, egg white is used for the first (complete intoxication) further intoxication is not elicited by the partial intoxicating substance, horse serum (G.P. No. 154). Similar results are obtained after sensitization with milk.

TABLE 5.

These guinea-pigs had been given one cubic centimeter of milk thirteen days previously.

G.P. No.	Date.	Given	Results.
81	March 30, 1908.	5 cc. horse serum subcutaneously.	Marked symptoms.
	March 31, 1908.	5 cc. milk intraperitoneally.	Marked symptoms.
80	March 30, 1908.	5 cc. milk subcutaneously.	Distinct symptoms.
	March 31, 1908.	5 cc. horse serum intraperitoneally.	Doubtful symptoms.

It is evident from these two tables that if the protein substances are given in a properly chosen order, namely, partially intoxicating followed by completely intoxicating, that a series of intoxications may be produced after sensitization by a single protein substance as well as after combined sensitization with several protein substances.

When we come to consider the results of successive intoxications after the combined anaphylaxis due to injection of a mixture of several proteids, we find that they are no more absolutely specific than are the intoxications just detailed, obtained after sensitization by a single proteid. A careful study of the results obtained both by Rosenau and Anderson and by ourselves shows distinctly that, in the case of simple anaphylaxis followed by intoxication with the same substance, the combination egg followed by egg is most toxic, and serum followed by serum the next most toxic, while the combination milk followed by milk is least toxic of all. When we consider the resultant intoxication by a given proteid we must consider, first, the relation of the intoxicating substance to the anaphylactizing substance, that is, whether homologous or not; and secondly, we must consider what the absolute intoxicating power of each proteid might be if an anaphylactin which was common to all the proteids used could be imagined. Such a "common" anaphylactin is, of course, purely hypothetical, but we may approach a condition such as might be caused by such a substance, by means of the "mixed" sensitization of Rosenau and Anderson. If we sensitize guinea-pigs with a mixture of horse serum, egg white, and milk they become capable of giving the maximum symptoms of intoxication with any one of these substances. If, however, they are given each substance in turn it is found that the chain of successive symptoms depends on the order in which the proteids are given.

TABLE 6.

These guinea-pigs were sensitized by subcutaneous injection of a mixture composed of horse serum .01 cubic centimeter, egg white one cubic centimeter, and milk one cubic centimeter. They were subsequently given doses of five cubic centimeters of each substance in turn at intervals of twenty-four hours, and in each case in a different sequence. Nos. 117, 118, 119 were injected beginning on the thirty-fifth day; and Nos. 76, 77, 78 were injected beginning on the fifteenth day; the two series, however, were judged to be comparable inasmuch as the relation of order of substances was considered in relation to the intoxication by the other substances which preceded or followed. The first two intoxications of a series were given subcutaneously, and the last one intraperitoneally.

G.P. No.	Order of Intoxicating Proteid.	Symptoms Corresponding to each Proteid.
76.......	*Egg;* horse serum; milk.	*Marked;* distinct; no symptoms.
118......	*Egg;* milk; horse serum.	*Severe*; doubtful; slight.
119......	Milk; *egg;* horse serum.	Severe; *severe;* marked.
78.......	Horse serum; *egg;* ×	Severe; *dead thirty minutes;* ×
77.......	Milk; horse serum; *egg.*	Severe; marked; *marked.*
117......	Horse serum; milk; *egg.*	Severe; slight; *severe.*

This table is arranged to emphasize the relation of the order in which egg white was placed in serial injection to the resulting symptoms which it caused. A composite table of the different proteids showing the relation of their order of injection to the symptoms which they caused follows:

TABLE 7.

Order of injection on subsequent days.

Proteid.	First Day.	Second Day.	Third Day.
Egg	Marked. Severe.	Severe. Death.	Marked. Severe.
Horse serum	Severe. Severe.	Distinct. Marked.	Slight. Marked.
Milk	Severe. Severe.	Doubtful. Slight.	None. ×

A consideration of these tables shows that after what may be termed a sensitization common to serum, egg, and milk, the initial injection of any one of these substances, after the proper incubation period, will cause maximum symptoms. If injected on the second day egg alone will cause as marked symptoms as if given first; horse serum has already lost part of its potency to intoxicate if given after either of the other proteids; and with milk the loss is greater still. On the third day egg has lost none of its potency, horse serum most of its potency, and milk no longer intoxicates. It is evident that these substances may be arranged in order of their absolute toxicity, egg white, serum, milk, which corresponds to their apparent value after homologous sensitization. And what is more important still is the fact that if, after the mixed sensitization (serum, plus egg, plus milk), the weakest intoxicating substance (milk) is given on the third day it awakens no symptoms. This is clearly evident also in the tables of Rosenau and Anderson. In other words, the reaction which it might have evoked if given early in the order can be in no sense specific since it has evidently been fulfilled by the other two substances.

No particular reference is here made to the pathology and histopathology of the intoxications by egg white, milk, and the serial intoxications produced by injection of the three substances. The lesions caused by these substances differ in details from those which we have described in pure horse serum anaphylaxis and will be considered at another time.

CONCLUSIONS.

The anaphylaxis in guinea-pigs caused by the previous injection of any one of the protein substances, horse serum, egg white, or milk, is only relatively specific. The maximum reaction on second injection is always obtained when the substance which has sensitized is used, but in certain combinations intoxication can be produced by the other two substances. This intoxication, by a heterologous proteid is "partial" and does not occur if the "complete" intoxication produced by the homologous proteid has been effected; when partial intoxication has been produced by one or both of the heterologous substances, complete intoxication may still be effected by the homologous substance. The intensity of an homologous intoxication, after anaphylaxis by a single substance, would seem to depend somewhat on the substance used, the order of toxicity ranging, egg white, serum, and last of all milk. After combined anaphylaxis, produced by initial injection of all three substances, the first intoxication, allowing of course a proper incubation period, may be produced by any one of the substances in question. When intoxications are effected with each substance in turn the serial set of symptoms varies according to the order in which the substances are injected on the subsequent days. When injected as the second or third of the series, egg white alone produces maximal symptoms at all times; horse serum is diminished in toxicity if used after either egg or milk and has lost markedly if used after intoxication with both substances. Milk is very slightly toxic if given second in order and absolutely non-toxic if given third. This would compare with the actual toxic power of each substance as noted after homologous sensitization.

The mixed anaphylaxis, moreover, is only relatively specific since egg and horse serum will completely preëmpt the possibility of intoxication by milk if this substance is given last.

BIBLIOGRAPHY.

1. Rosenau and Anderson. A study of the cause of sudden death following the injection of horse serum. Bull. No. 29, Hyg. Lab., U.S. Pub. Health and Mar. Hosp. Serv., Washington.

2. Rosenau and Anderson. Studies upon hypersusceptibility and immunity. Bull. No. 36, Hyg. Lab., U.S. Pub. Health and Mar. Hosp. Serv., Washington.

3. Rosenau and Anderson. The specific nature of anaphylaxis. Jour. of Infect. Diseases, iv, 1907, 552.

4. Gay and Southard. On serum anaphylaxis in the guinea-pig. Jour. Med. Research, xvi, 1907, 143.

5. Gay and Southard. Further studies in anaphylaxis: I. On the mechanism of serum anaphylaxis and intoxication in the guinea-pig Jour. Med. Research, xviii, 1908, 407.

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FURTHER STUDIES IN ANAPHYLAXIS.*

IV. *The Localization of Cell and Tissue Anaphylaxis in the Guinea-pig, with Observations on the Cause of Death in Serum Intoxication.*

F. P. Gay and E. E. Southard.

(*From the Pathological Laboratories of the Harvard Medical School and the Danvers Insane Hospital.*)

I. The gross lesions of serum intoxication in the guinea-pig. — In 1907 we reported the occurrence of characteristic hemorrhages in guinea-pigs which had received a second properly timed dose of horse serum.[1] We observed such hemorrhages both in those guinea-pigs which died of the intoxication and in those which we killed at various intervals after intoxication. The hemorrhages were not quite constant in occurrence, but were found in one or more organs in thirty-four out of forty-one guinea-pigs autopsied at intervals within the first twenty-four hours after injection. The hemorrhages occurred in a great variety of organs. The most massive hemorrhages, and those most frequently observed, took place in the stomach wall. Thus we found gastric hemorrhages in thirty-two of the forty-one guinea-pigs examined within twenty-four hours of the toxic injection.

Further observations[2] bring our numbers to a total of eighty-six guinea-pigs with hemorrhages in one or more organs, five with doubtful hemorrhages, eleven without hemorrhages in a series of one hundred and two guinea-pigs examined within twenty-four hours of the toxic injection. Fifty-nine of these guinea-pigs (besides three doubtful) showed gastric hemorrhages. We have three new localizations of hemorrhage to report, the brain (three cases), the peritoneum (two cases), the spinal cord (one case).

Hemorrhages were localized in the complete series (1907 and 1908) as follows: Stomach, 59; lungs, 41; heart, 15;

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cecum, 9; spleen, 9; adrenal, 8; kidney, 4; muscle, 3; lymph node, 3; brain, 3; diaphragm, 2; liver, 2; pericardium, 2; peritoneum, 2; thyroid, 2; spinal cord, 1.

The occurrence of these gross lesions (in eighty-five per cent of our series of guinea-pigs) escaped the attention of the initial writers on anaphylaxis of this type (Otto in Ehrlich's laboratory, and Rosenau and Anderson in the U.S. Hygienic Laboratory). Otto, in fact, in his first paper[3] specifically denied the occurrence of macroscopic lesions in serum intoxication, and Rosenau and Anderson[4, 5, 6, 7] nowhere state the observation of macroscopic or other lesions in the disease. Lewis,[8] however, working under the direction of Theobald Smith is able to confirm our observations fully and states that Smith, one of the earliest observers of anaphylaxis of this type, had seen such lesions in intoxicated guinea-pigs several years before. Since these publications, there has been neither confirmation nor denial of these findings. Besredka[9] remarks that our structural findings may in the future be of service in clearing up the mechanism of the disease.

As we showed in 1907, these lesions have an important bearing on hypotheses concerning serum intoxication. We showed by an extensive histological study that the gross lesions are only indicators of a manifold series of cell-reactions, involving changes in capillary endothelium, voluntary and cardiac muscle fibers, nerve fibers, and gastric epithelium. As with the gross lesions, the microscopic lesions are distinguished by their focal distribution. This focality extends down to the separate cells, in such wise that single nerve fibers and single muscle fibers are found in a state of extreme or maximal fatty change in the midst of wholly normal fibers.

What is the significance of these lesions? The lesions cannot be regarded as anatomically specific for the serum disease. They belong in the same logical group with the multiple focal hemorrhages of the exanthems, of purpura, and of urticaria. They have much in common with hemorrhages due to local endotheliolysis produced by the application of such substances as venom. Can the reactions be proved by histological methods to show anything histologically or cytologically specific for the serum disease? This question must be answered in the negative. There is nothing in the lesions of this serum disease which approaches a tubercle or a small-pox vesicle in specificity. The importance of our structural observations does not consist in a demonstration of specific lesions, but in the exact demonstration of one method of producing lesions that are common in various types of disease, particularly in the exanthemata.

2. The cause of death in serum intoxication. — A complete delineation of this kind of pathogenesis would comprise: (1) modifications of tissue during the stage of preparation (anaphylactic phase), (2) the lesions of intoxication (critical toxic phase), and (3) the phenomena of repair and secondary anaphylaxis (reparative and secondary anaphylactic phases). In our former paper we confined ourselves largely to the lesions in the critical phase of intoxication, noting that the primary anaphylactic phase yielded few structural data open to observation. In the present communication we offer a continuation of our structural studies, embracing a more particular account of the cause of death in the critical phase, in the light of which some further observations on the anaphylactic and reparative phases are considered. Nothing is more striking than the sudden death following toxic injection by way of the carotid artery or jugular vein. The hemorrhages in brain, lungs, and heart, produced by such toxic injections, do not admit a purely mechanical explanation, since they are absent in control unused pigs injected with the same amounts of horse serum.

The local fatty changes in the capillary endothelium near the hemorrhagic areas in the heart muscle in these experiments must be closely related to the genesis of the hemorrhages.

'But, although striking, these lesions are, in the strict sense, hardly lethal. What is the cause of death in the critical phase?

Hypotheses concerning the cause of death in the critical phase are in the field as follows:

1. *The functional hypothesis.* — Lewis[10] thinks the cause of death in the critical phase depends on "the disordered function of a single organ, or broken coördination between several organs." The hypothesis, as stated, gives no clue to the nature of the functional disorder, or to the organ or organs involved. Lewis leaves in doubt whether the intoxication affects the nervous system or the heart or the lungs, or the heart and lungs through the nervous system. The manifold lesions are admitted, but these lesions are not regarded as pertinent to the occurrence of the functional disorders. It does not appear that this hypothesis is more than a restatement of what occurs in the symptomatic course of the disease, or much more than a blank form for whatever might occur in the process.

2. *The latent brain lesion hypothesis.* — This hypothesis was constructed by Besredka and Steinhardt[11] at the outset of their work. They suppose that the sensitized guinea-pig acquires and retains a latent lesion in its brain. The toxic injection serves to start up (réveiller) the latent brain lesion, bringing about severe disturbances or death. If we substitute for the term lesion (with its structural connotations) the term condition (without such specialized connotations), it is evident that the hypothesis of Besredka and Steinhardt involves scarcely more than the assumption that the symptoms of death in the critical phase are effected through the specially sensitized brain. This hypothesis is, therefore, an advance upon Lewis' functional hypothesis in that Besredka and Steinhardt particularize the supposed source of the disordered functions. Although this hypothesis is not sufficient to explain the lesions of remote organs (such as stomach or cecum since described by us), the hypothesis may contain some truth in so far as it applies to some of the prominent and apparently fatal symptoms. The functional hypothesis of Lewis and the latent brain lesion hypothesis of Besredka have, therefore, much in common; but Besredka indicates

the single organ whose disordered function comes prominently into play.

3. *The hypothesis of specific toxic action upon the respiratory centers.* — There is no doubt that the cause of death is often a respiratory one. From such symptomatic observations, Rosenau and Anderson suggest that we here deal with a poison causing death through the nervous control of the respiration. In order to exclude local effects upon the diaphragm, Rosenau and Anderson[12] showed that the phrenic nerve after death is still excitable, and produces diaphragmatic movements on electrical stimulation after death. Vaughan and Wheeler,[13] dealing with similar considerations in poisoning by white of egg, also maintain that the poisonous substance owes its toxicity to a combination with the cells of the respiratory center. Rosenau and Anderson have since[14] generalized their original suggestion, proposing that "profound chemical changes, perhaps in the central nerve cells, are probably produced by the first injection." In a later paper[15] these writers further maintain that the phenomena of the critical phase are also explained by profound chemical changes, probably in the nervous system. It appears from this work, as well as from our own constant observation (see below) of pulmonary emphysema in those pigs which die rapidly, that the respiratory center, or, at any rate, the nervous respiratory apparatus, is prominently affected by the toxic injection. But, as appears from further considerations, this toxic action upon the respiratory center (or nervous apparatus) cannot be regarded as specific.

Briefly, then, the functional hypothesis of Lewis is scarcely more than a hypothesis in name, since it does no more than restate the problem; the latent brain lesion hypothesis of Besredka lacks a convincing demonstration of either the morphological or the chemical nature of the lesions, either before or after they are "réveillé" by the toxic injection; and the respiratory center hypothesis, as first advanced by Rosenau and Anderson, has considerable evidence in its favor, explains the direct cause of death in most or all instances, and merely errs in suggesting that the toxic substance is a specific respiratory poison.

Our work to the present time has shown that pulmonary emphysema is a constant feature at autopsy in guinea-pigs dying quickly after the second or toxic injection. We are inclined to regard this emphysema as the effective cause of death in the quickly fatal cases. Of course, the pulmonary hemorrhages and cardiac hemorrhages, which we were able to produce by toxic jugular injections with death in four minutes, are important factors as against possible recovery from emphysema in certain highly intoxicated guinea-pigs.

What is the mechanism of this fatal acute emphysema in the intoxicated guinea-pigs? The emphysema is an expression of death in the inspiratory phase with diaphragmatic spasm. All evidence at hand indicates that the diaphragm is under a constant nervous stimulation of excessive degree during the critical phase following the toxic injection. The probable course of the impulses which produce this hyperstimulation of the diaphragm is by way of the respiratory center in the medulla to the phrenic center in the cervical spinal cord and thence through the phrenic nerve.

Our recent experiments with sensitized guinea-pigs bring out the fact that the more readily the horse serum on the second injection can gain access to the nervous respiratory apparatus, the more certainly will excessive and spasmodic diaphragmatic and general respiratory contractions ensue. The fatalities upon injection of serum into the fluid spaces about the brain (we have preferred the post-orbital route for injection) and into the spaces about the spinal cord (notably in the upper cervical region) are very frequent, and with toxic doses of one cubic centimeter, practically constant.

We shall not here report in detail the results of all our localized inoculations with respect to their differential effects upon the nervous apparatus at large, reserving these findings for special neuropathological consideration. The effects of injections in the vicinity of various parts of the central nervous system are to a great degree differential, and may prove of some importance in determining special reactions of different regions, especially in the spinal cord. The effect upon the respiratory center is marked and early.

The simplest explanation of this effect is that the toxic factor of the horse serum in these local injections comes directly into contact with the properly sensitized nervous apparatus of respiration, and causes it to work excessively. As is well known, expiration is, under ordinary conditions, a purely mechanical matter; but inspiration is under nervous control. Excessive stimulation of the phrenic center leads to death in the inspiratory phase. Even after opening the thorax and excision of the heart and lungs, intense diaphragmatic contractions may be observed in guinea-pigs dying in the critical phase.

It has so far been impossible for us to determine which portion of the respiratory nervous apparatus is most highly sensitized, or whether any portion is more highly sensitized than another.

It is clear, however, that the hyperstimulation may in some instances be effected over two or three separate conducting elements or neurones. A striking experiment, recently accomplished, consists in the production of respiratory symptoms by touching the vagus nerve (lifted from contact with surrounding structures) of a sensitized pig with a pledget of cotton soaked in horse serum. The same procedure in non-sensitized pigs fails to evoke characteristic diaphragmatic contractions, and salt solution fails to produce the effect in sensitized animals.

This experiment would seem to indicate that the vagus nerve is to some extent sensitized in the general anaphylaxis. We have so far been unable to produce death by this procedure. Fatal issue seems to require immediate stimulation of the medullary or phrenic centers, and, so far, we are unable to report finally which of these centers is the more highly sensitized. Experiments to solve these questions are difficult, because it is desirable to avoid mechanical injury to the centers, but at the same time secure quick absorption of toxic serum by a given center, and distinguish the effects of the local anaphylaxis from those of anaphylaxis in the rest of the body which the serum speedily invades by blood or lymph.

Our vagus experiments may serve for the present to indicate the line of attack on the problems of local anaphylaxis and to bring out the mechanism of one of the most violent and striking of the symptoms of the serum disease. And our local injections with object of differentially intoxicating different parts of sensitized nervous system (to be reported in detail in a later study) serve simply to bring out the strikingly variable accessibility of the respiratory center, when properly prepared, to a poison injected at different points with relation to the nervous system.

Therefore we desire to substitute, for the theories of the cause of death in the serum disease as so far proposed, and above enumerated, a theory of local anaphylaxis of the respiratory nervous centers. By this we mean a condition induced in the respiratory centers, by means of anaphylactin in the fluid media bathing their cells, such that their elements are excessively stimulated when brought in contact with the toxic or assimilable factor of horse serum. The cause of death is, therefore, an indirect one, being founded on hyperstimulation of the phrenic nerve and cessation of respiration in the inspiratory phase. On this hypothesis the means of avoiding death in the critical phase of intoxication following anaphylaxis would be a therapeutic agent depressing the respiratory centers.

This hypothesis differs essentially from those previously proposed. So far from being due to a disorder of function or incoördination between organs, as proposed by Lewis, the cause of death would seem to be due to an excess of functioning of an apparatus, which is working quite properly in response to the stimulation it receives. The new hypothesis is also more specific than the hypotheses of Lewis and of Besredka. Nor is it necessary to suppose with Besredka a latent brain lesion which is started up once more by the second injection. Rather should we say that a condition had been induced in these cells, as a result of placing an anaphylactic substance in their surrounding media, such that certain results follow upon injection of a toxic substance. There is an essential difference between the idea of slight irritation followed by severe irritation of qualitatively the same character (as indicated by Besredka's metaphor, "réveiller") and the idea which we support that a substance (anaphylactin) bathing, among other structures, the respiratory nerve cells, has the capacity of altering those cells so that a second substance (normally ineffective) can become effective in stimulating them.

It is obvious that our hypothesis has much in common with any which supposes a specific action upon respiratory centers. And, if Rosenau and Anderson were to ground their hypothesis upon the rendering of these centers specifically accessible to certain toxic substances, we should agree with them. But it seems rather that they suppose that a specific toxine has been produced in the process of anaphylaxis or that a toxine is produced by the union of serum constituents and antibodies,[16] such that the wholly unaltered respiratory center can now be affected by this specific toxine. Whereas Rosenau and Anderson suppose a specific respiratory toxine to be somehow newly produced, we prefer to suppose that the anaphylactin of the first injection has altered certain properties of the cells.

Meantime, the insistence of Besredka upon "latent brain lesions" and of Rosenau and Anderson upon "profound chemical changes perhaps in the central nerve cells" is an indication that these workers fundamentally agree that we must look to the cells for the explanation of much of this problem. It does not seem that Rosenau and Anderson would be forced to hint at profound chemical changes in the cells, if the antibody hypothesis were quite convincing.

A consideration of the cause of death, with cessation of respiration in the inspiratory phase under the influence of respiratory central intoxication, which we can hasten by suitable application of serum near those centers, leads us, therefore, to the conception of a local acquired anaphylaxis or specific lowered resistance of these centers, under the influence of one substance (anaphylactin) so that they become hypersusceptible to another substance (toxic factor).

An extension of these conceptions to the rest of the body requires separate consideration.

3. Tissue anaphylaxis. — We have so far considered two striking features of the critical phase after the second injection, viz.: The multiple focal hemorrhages frequently found at autopsy within twenty-four hours of the toxic injection and the fatal issue which, when it follows, occurs usually within an hour of the toxic injection. We have not found that either of these features is absolutely constant, although our percentage of hemorrhages (eighty-five per cent) is enough to demonstrate their importance, although the fatal issue seems to vary, roughly at least, with the speed and volume with which the horse serum reaches some portion of the respiratory nervous apparatus. We shall later communicate work on the localization and dosage of respiratory central intoxication.

Is there some broader conception under which these two striking features of the critical phase can be united? Further work upon the histological features of the critical phase confirms the opinion expressed in our paper of 1907[17] that focal fatty changes are found in very numerous tissues of several different sorts. Some of these changes, especially when several altered cells are in close spatial relation, offer loci of lowered resistance permitting hemorrhages. But it is not at all necessary that the altered cells shall be so grouped as to allow hemorrhages. Take the stomach, for example, in which the most frequent and massive hemorrhages and hemorrhagic ulcerations occur: much more frequent than the hemorrhagic areas in these stomachs are areas in which fatty changes of sharply definite character but without hemorrhages are found.

The focal fatty changes of the critical phase are of more fundamental importance than the hemorrhages, which are possibly but the mechanical expression of *loci minoris resistentiæ*.

Since our former work, we have studied in particular the tissues of guinea-pigs in various stages of recovery from intoxication and during secondary anaphylaxis, as well as the conditions of second and third intoxications.[18] The result of this work has been to confirm the former findings and to show that the disease is essentially a critical one.

The toxic injection can be said to effect no further disturbance than that of the first hour. Though this could have been surmised from the symptoms, still it might be regarded as likely that some further phenomena would characterize the tissues.

We thought, in particular, that an investigation of the blood picture during the course of the disease might exhibit the tissue reactions more exactly.* This work so far indicates that the same type of reaction — hypoleucocytosis followed by hyperleucocytosis — occurs upon injection of horse serum into normal as into sensitized animals. This fact precludes extraordinary stress being laid at this time upon the leucocyte counts in this disease. The difficulty in drawing blood from guinea-pig ears during the critical phase is an interesting point, which may depend upon contraction of peripheral vessels due to an intoxication of the nervous system.

Although it is true that definite blood alterations do follow the toxic injection, it may be suspected that these alterations have to do merely with the elimination of horse serum and with readjustment of the blood cell supply and that they occur in normal animals in similar fashion after serum injections. A study of the spleens of the guinea-pigs, killed at various intervals of hours and days after the toxic injection, demonstrates that in less than six hours the spleen spaces become filled with polynuclear leucocytes. This tendency is so considerable that the spleens may become visibly swollen. This swelling is only in part due to congestion with blood corpuscles. The intrasplenic leucocytosis is prominent still in guinea-pigs killed at intervals up to twenty-four hours after the toxic injection, but in most cases gradually disappears and gives place to mononuclear phagocytosis during the third day. Some guinea-pigs on the fourth day yield little sign in their spleens of the toxic injection; but in some a moderate leucocyte destruction is somewhat persistent. But although a detailed study is contemplated of the conditions of the peripheral and splenic leucocytosis as well as of marrow conditions, it seems at present, from the orienting examinations already performed, that the relation of these pictures to the process of tissue anaphylaxis is quite obscure and that the body exhibits the same signs of eliminative effort in the blood after the first injection as after the toxic injection. In view of our study of recurrent anaphylaxis [19] in the same animal, these findings become interesting, but it is premature to state that the blood reactions have any relation to the process of anaphylaxis.

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* This was undertaken by Dr. M. M. Canavan of the Danvers Insane Hospital, who proposes to contribute the findings in detail shortly.

These studies may serve to show, therefore, that tissue anaphylaxis is very possibly not at all a function of the blood, detectable by cell changes therein. The reactions, both structural and functional, of the critical phase indicate that very numerous tissues of several orders have been altered in anaphylaxis.

What can be found in these tissues during the stage of anaphylaxis? It will be remembered that the only striking changes which we found in the anaphylactic phase in our former work were certain changes in the peripheral nerves and spinal cord, decidedly less often in nerve tissues above the medulla. These changes consisted in blackenings of scattered myelin sheaths demonstrable in Marchi preparations. The alterations were of two sorts, which we termed respectively linear and nodal changes. The linear blackenings, which exhibit the affected fiber as replaced by a row of black globules and signify a severe injury reparable only by regeneration, were decidedly less frequent than the nodal blackenings. The nodal blackenings, found in the peripheral nerves characteristically, show a limited osmic acid impregnation confined to the regions of Ranvier's nodes in a given fiber. These nodal changes are regarded as quite consistent with rapid recovery of normal conditions in the affected sheaths. It is possible that conduction is not interrupted by such changes but is altered in ways not now definable.

In addition to these myelin sheaths changes there are other and possibly correlative changes in nerve cells demonstrable by the Nissl method after alcohol fixation. We regarded these as within the limits of technical error, but, so far as reliable, consistent with prodromata toward the well known axonal reaction.

We were not eager to regard these changes as indicative of the latent brain lesions of Besredka or of the profound chemical changes of the nervous system proposed on theoretical grounds by Rosenau and Anderson, and, although we have worked much on this problem since and in particular with the sensitizing euglobulins of Gay and Adler, we are still unwilling to say that our findings represent the essential changes of the anaphylactic phase.

In the first place, we have found similar changes in seemingly normal material, and especially in the diphtheria toxone-paralysis material kindly given to one of us by Theobald Smith. It may be that these changes are simply indices of the extreme lability of nerve tissue, meaning by this lability a capacity for relatively rapid physical alterations of nerve cell and nerve fiber, demonstrable by osmic acid and methylene blue methods.

In the second place, our orienting work with the blood pictures in this disease indicates that to some extent the same species of leucocyte variation is present in the anaphylactic phase as in the toxic phase. So many substances are undoubtedly present in horse serum that the chance of changes effected by other constituents than the sensitizing or intoxicating constituents must be strongly considered. It is possible, therefore, that these anaphylactic nerve cell and fiber changes are purely incidental to the action of unrecognized constituents of horse serum.

Work is in progress with the relatively pure sensitizing substances (euglobulins of Gay and Adler) to discover what differential effects these substances may bring out.

One further word concerning the relation of the fatty changes and hemorrhages of the toxic phase and possible antecedent changes in the anaphylactic phase. Critics have suggested to us that possibly at some time during the anaphylactic phase fatty changes supervene in various foci in various organs, and that the hemorrhages of the toxic phase are simply mechanical expressions of local acquired weaknesses in the vessels. This hypothesis would suggest that horse serum can in the first instance produce qualitatively the same kind of visible changes which characterize the toxic phase. We have made further examinations of the tissues in large numbers of guinea-pigs. The anaphylactic phase is not characterized by such changes. Using the stomach wall as a histologically pure field for this study, we have yet to find, in any pig killed in the anaphylactic phase, convincing evidence of the presence of intraepithelial fat, vascular fat, or early necroses of epithelium under the influence of anaphylactin.

These statements may be generalized as follows: The essential cytological features of the process of anaphylaxis have yet to be discovered. They do not consist in a minor degree of those changes (focal cytolyses) which characterize the tissues in the toxic phase. The process of anaphylaxis is not a cumulative process, and the toxic phase is not the result of a summation of similar stimuli or effects.

Certain changes, expressive of the extreme lability of nervous structures, have been found in the anaphylactic phase in peripheral nerves and spinal cord. These changes may or may not represent essential features of the process of anaphylaxis. The nervous system is not a clear field, histologically speaking, for the study of minor fatty changes, since these may be the expression of numerous uncontrollable conditions. So far as the changes discovered have any bearing, the alterations produced by anaphylaxis may be regarded as of a physical nature, permitting speedy rearrangement of various contained substances.

Focal histolyses are not the rule in the toxic phase. Separate cells are more likely to be prepared for intoxication and to succumb thereto (focal cytanaphylaxis followed by focal cytolysis). But the diffuse changes in the stomach wall indicate that focal histanaphylaxis followed by focal histolysis may be the rule under some conditions (effect of gastric juice, etc.). Experience with the critical phase indicates that the cells of certain physiological centers may become highly sensitized (cell group anaphylaxis), and that the functional expression of their intoxication may lead to severe symptoms or fatal results.

4. The reparative phase and recurrent anaphylaxis. — We mentioned in our paper of 1907 that the serum disease might be repeated, and expressed the hope that by suitable repetitions chronic conditions would be produced. This hope has not been realized. The lesions do not necessarily repeat themselves in the site of the original lesions or even in neighboring situations. We have not carried our histological work beyond the reparative stages of tertiary intoxication.

Fresh intoxication in new sites is the rule in secondary or tertiary intoxications. But the repetition is virtually a new instance of the old disease and, certainly in the majority of instances, does not effect a cumulative action upon structures formerly attacked.

We hoped to find in the stomach instances of fresh intoxication superimposed on the remains of old and to discover that recurrent anaphylaxis would emphasize that of the sites formerly sensitized. The stomach seemed to be a likely seat for this cumulative anaphylaxis imagined by us, because of the tendency of the stomach to yield focal histolyses instead of the cytolyses of numerous other organs.

We thought that the new areas of local anaphylaxis might to some extent coincide with or overlap the old areas of histolysis and lead perhaps to chronic ulceration. But, so far, the conditions have not fulfilled such preconceptions.

This branch of the work, therefore, brings out indirectly the features of the anaphylactin hypothesis. It is the habit of the anaphylactin to sensitize focally certain cells or cell groups. The same anaphylactin in recurrent anaphylaxis is disposed to a similar focal sensitization in which, however, fresh elements are affected.

In those cases of cell group anaphylaxis, after which intoxication expresses itself largely in a functional manner (as in local respiratory center anaphylaxis), a repetition of similar toxic effects can be produced. There was no tendency for repeatedly intoxicated pigs to diminish the severity of their respiratory symptoms. It is possible that, on this line of attack, cumulative effects could be eventually demonstrated in certain centers. It is also possible that separate cells of the respiratory centers are always newly involved in recurrent anaphylaxis and repeated intoxication, and that the toxic effects are not due to activities of the same individual members of the cell group involved. These hypotheses, however, evidently transcend the range of immediate proof.

CONCLUSIONS.

The results of this work are in part confirmatory of our previous results and consist in part of novel data.

Eighty-five per cent of guinea-pigs which, after sensitization with horse serum and intoxication by a second dose of horse serum, die in the critical phase or are killed within twenty-four hours of the second injection, exhibit macroscopic hemorrhages in one or more organs. The stomach leads the other organs in frequency of involvement (fifty-eight per cent); the lungs stand next (forty per cent). Three unusual localizations of hemorrhage, not noted in our previous paper, are brain, spinal cord, peritoneum.

The cause of death, when it occurs, is respiratory. Respiration ceases in the inspiratory phase and shows itself anatomically and histologically as emphysema. Death does not occur, as a result of this disease, except in a critical phase which occupies at most one hour.

The most striking functional feature of the critical phase, after the second or toxic injection of horse serum, is severe diaphragmatic spasm. The spasms are often accompanied by similar shock-like spasms of the accessory inspiratory muscles and of other trunk and limb muscles.

The most rapid deaths are produced by intracarotid, intrajugular, post-orbital, and paraneuraxial injections. The occurrence and rapidity of death in the critical phase, as well as the severity of respiratory symptoms throughout the toxic phase, appear to vary with the nearness of the toxic injections to the respiratory central apparatus.

A new line of research is opened up by the paraneuraxial injections of horse serum in sensitized guinea-pigs. These seem to prove that differential irritative and paralytic reactions can be secured by small localized injections of horse serum adjacent to various parts of the sensitized central nervous axis.

Severe respiratory symptoms can be produced in sensitized (but not in normal) guinea-pigs by local applications of horse serum (not by salt solution) to the exposed vagus. This is interpreted to signify a conveyance of impulses over at least three neurones to the diaphragm, that is, to the medulla, thence to the phrenic center, and thence to the diaphragm. We have not produced death by these vagal applications of horse serum.

To explain these respiratory symptoms, we offer an hypothesis of local tissue anaphylaxis expressed in a relatively specific sensitization of the respiratory centers. We regard as unfounded those hypotheses which consider the respiratory (and other) centers and tissues as unaltered in the anaphylactic or sensitizing phase, and which allege the manufacture of antibodies in the blood serum which later unite with the second dose of horse serum to form new specific respiratory toxines. We regard this change induced in the respiratory centers as of a physical rather than a chemical nature, so far as this distinction is of importance in this connection.

Neither hemorrhage nor respiratory death is an indispensable feature of this disease. Some guinea-pigs show no hemorrhages. Some show slight symptoms. The hemorrhages do not vary in frequency or extent with the severity of the symptoms in all cases.

But all guinea-pigs so far examined in the toxic phase do show focal fatty changes in many tissues of several genetic types. These changes are, in many regions, of an extremely focal character, involving often a single muscle fiber, nerve-fiber, or other cell, as the case may be. The toxic phase is characterized by focal cytolyses of wide distribution. Except in areas of hemorrhage (where local mechanical destruction complicates findings) and in certain diffuse fatty changes in the gastric epithelium (where the local action of the gastric juice may come in play), groups of contiguous cells are not characteristically affected by fatty change: focal histolysis is not the rule.

And, if focal cytolysis (rather than focal histolysis) is the rule in the toxic phase, then it appears that the work of the anaphylactic phase is to sensitize cells in a variable degree (rather than to sensitize several contiguous or regionary cells in a like degree).

BIBLIOGRAPHY.

1. Gay and Southard. On serum anaphylaxis in the guinea-pig. Journ. Med. Research, xvi, 1907, 143.

2. Gay and Southard. Further studies in anaphylaxis. I. On the mechanism of serum anaphylaxis and intoxication in the guinea-pig. Journ. Med. Research, xviii, 1908, 407.

3. Otto. Das Theobald Smith, sche Phaenomen der Serumüberempfindlichkeit. Leuthold Gedenkschrift, i, Berlin, 1906.

4. Rosenau and Anderson. A study of the cause of death following the injection of horse serum. Bull. No. 29, Hyg. Lab., U.S. Pub. Health and Mar. Hosp. Service, Washington, 1906.

5. Rosenau and Anderson. Studies upon hypersusceptibility and immunity. Bull. No. 36, ibid., 1907.

6. Rosenau and Anderson. The specific nature of anaphylaxis. Journ. Infect. Diseases, iv, 1907, 552.

7. Rosenau and Anderson. A review of anaphylaxis, with especial reference to immunity. Ibid., v, 1908, 85.

8. Lewis. The induced susceptibility of the guinea-pig to the toxic action of the blood serum of the horse. Journ. Exper. Med., x, 1908, 1.

9. Besredka. Review in Bull. de l'Inst. Pasteur, v, 1907, 850–852.

10. Lewis. Loc. cit., *vide* general discussion, ad fin.

11. Besredka et Steinhardt. De l'anaphylaxie et de l'anti-anaphylaxie vis-à-vis du serum de cheval. Ann. de l'Inst. Pasteur, xxi, 1907, v, 119.

12. Rosenau and Anderson. v. Reference 4, 14, 15.

13. Vaughan and Wheeler. The effects of egg-white and its split products on animals. Journ. Infect. Diseases, iv, 1907, 504.

14. Rosenau and Anderson. v. Reference 5. Part xii.

15. Rosenau and Anderson. v. Reference 7, 97.

16. Gay and Southard. v. Reference 2.

17. Gay and Southard. v. Reference 1, 161–171.

18. Gay and Southard. Further studies in anaphylaxis. II. On recurrent anaphylaxis and repeated intoxication in guinea-pigs by means of horse serum. Journ. Med. Research, xix, 1908, 1.

19. Gay and Southard. v. Reference 18.

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A PATHOLOGICAL STUDY OF A CASE OF HYDROCEPHALUS.

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(*From the Laboratory of the Danvers Insane Hospital, Hathorne, Mass.*)

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The following case is that of a hydrocephalic who lived to the age of 46 years. During his stay in the hospital he was practically an imbecile and had never been able to do any work. His history as given by his father records his advancement in school as far as the master's room (corresponding to the eighth grade) at the age of sixteen. The examination of the brain has been an attempt to homologize the surface anatomy with the normal, and following the work of Campbell one hemicerebrum has been studied to define the distribution and to compare the cell lamination and fiber arrangement of the various types of cortex.

The work was done in the laboratory of the Danvers Insane Hospital, Hathorne, Mass., during the months of January and February, 1907. The author wishes to express his thanks to Dr. E. E. Southard, Pathologist to the Danvers Hospital, for his direction, aid and suggestions and to Dr. Chas. W. Page, Superintendent of that institution, for the opportunity to work in the hospital laboratory.

HISTORY.

By Dr. H. M. Swift, Assistant Physician, Danvers Insane Hospital.

C. W. H. White male, æt. 45. Born in Salem, Mass., of American parents. Admitted to Danvers Insane Hospital October 13, 1905. Died January 24, 1906. Diagnosis: Imbecility (hydrocephalus).

Family History.—Father alive and well at the age of 76. Mother well. One brother living and well. One sister died at the age of three weeks. (Assigned cause, jaundice.)

Previous History.—Had all the diseases of childhood. Typhoid several years ago.

Has never used alcohol or tobacco. In school he went as far as the master's room but father does not think he was promoted every year. Left school at the age of sixteen and has never done any work since except errands around the house. Has always been ailing with some minor physical disability.

Present Illness.—He has never been allowed to go out of the house without an attendant; but on September 25 he left home unobserved and was gone all night, returning exhausted and unable to tell where he had been. Memory has been getting weaker of late years and he has shown signs of gradual mental degeneration. He has lately been more irritable and shows an increasing desire to get away from home. Never violent.

Physical Examination.

Examination by Dr. H. M. Swift.

Height, 5 feet 7 inches. Weight, 137 pounds. Poorly developed and poorly nourished. Head very large (circumference 25¼ inches). Face long, narrow and wedge-shaped. Right shoulder narrower and higher than left. Tendency to knock-knee.

Neurological Examination.

Neuromuscular Condition.—No swaying in Romberg's position. Gait fairly steady. Coarse tremor of fingers. Tongue protruded steadily and in the midline.

Vision and Hearing.—Apparently normal.

Reflexes.—Left pupil is slightly irregular and there is practically no reaction. Knee-jerks quite lively. Suggestion of clonus in left knee. Achilles brisk with slight clonus in both ankles. Arm reflexes very lively. Abdominal and cremasteric not marked.

Sensation.—Patient makes many mistakes in differentiating between sharp and dull points.

School Knowledge.—Repeats alphabet, names of the months and days of the week correctly. Counts one to 50 without error. Elementary arithmetic problems are for the most part wrongly answered although there is some evidence of retention of knowledge in this particular. His handwriting when asked to write his name is a scrawl in which the name Charles and an occasional other letter all that is legible.

Appearance and Attitude.—Slow listless manner. Responds only to direct questions. Volunteers nothing. Sits by himself. Idle. Has to be urged to do anything. No interest in surroundings.

Speech.—Talks slowly. Test phrases repeated incorrectly.

Orientation.—Very poor. Thinks the year is 1870. Knows he is in a hospital but doesn't know what kind or where.

Hallucinations.—None evident.

Memory.—Practically no memory for recent or remote events.

Association.—There is considerable limitation in range of thought and lack of ideation.

Judgment.—No delusions. No insight.

Emotions.—Indifferent and apathetic. Occasionally slightly irritable.

Will.—No motor excitement or marked will disturbance.

Social Relations.—Quiet, tidy and orderly.

A few weeks before death the patient developed decubitus, ran a slight temperature and became stupid and lethargic.

Autopsy Record.

Autopsy six hours post mortem. January 24, 1906. Head, body and cord by Dr. E. E. Southard.

External Examination.—White male of middle height. Skull symmetrically enlarged, leaving face relatively small. Trunk and extremities of normal build. Body warm. Trace of lividity of dependent parts. No edema. Pupils not dilated. Abdominal subcutaneous fat 1.5 cm. thick.

Cavities of Trunk.—Normal. Mesenteric lymph nodes not palpable.

Heart.—Wt. 230 gms. Epicardium contains a moderate amount of fat. Myocardium firm and red. Endocardium and valves normal.

Spleen.—Wt. 105 gms. Capsule smooth. Substance firm and dark red. Trabeculæ normal or slightly increased. Malpighian bodies hard to make out.

Lungs.—Strikingly free from carbon markings. A few rounded collections of carbon in widely separated foci. Posterior parts of lungs edematous and congested. Left apex shows a smooth rounded fibrous capsule about 3 mm. deep under which the lung tissue is apparently normal. Bronchi and bronchial lymph nodes normal.

Gastrointestinal Tract.—Normal.

Pancreas.—Normal.

Liver.—Wt. 1050 gms. Normal.

Gall Bladder.—Single walnut-sized calculus. Wall normal, ducts patent.

Adrenals.—Normal.

Kidneys.—Wt. 220 gms. Strip well. Substance normal. Pelves and ureters normal.

Bladder and Prostate.—Normal.

Testes.—Thread well.

Aorta.—Shows slight sclerosis with puckering of arch.

Organs of Neck.—Normal.

Head.—Hair grey and thin. Scalp strips readily. Calvarium thin. No diploë. Dura not adherent to calvarium. Dura distended. Sinuses contain liquid blood. Arachnoid villi moderate in amount. Dura strips readily from pia except over ascending frontal gyri where, particularly on the left side, the dura and pia are gummed together by a plastic stringy yellowish-grey exudate, covering an area on each side scarcely larger than a dollar and thinning out gradually at the edges. There is no gross connection between this exudate and the otitis media of the right side. Except at the vertex the pia is without exudate or edema and shows a few fibrous streaks over sulcal veins. The substance of the brain, cerebellum, interbrain, pons and bulb, exclusive of the fluid contained in the ventricles, weighs 960 grams. The fluid withdrawn from the ventricles measures 1300 cc. The sulcation of the brain is rich but chiefly superficial. Many of the sulci run inwards for a few mm. and bend at right angles, assuming a position concentric with the hemisphere surface for a few mm. Incision of the ventricles and withdrawal of the contained clear fluid shows basal structures of a normal appearance but marked attenuation of the callosal and fornix tissue. The cerebellum is of normal appearance and consistence. Lower structures grossly normal. The right middle ear contains semi-liquid yellowish-green pus communicating with a cavity 1.5 cm. in diameter in the mastoid process.

Anatomical Diagnoses.—Purulent otitis media; localized purulent leptomeningitis (vertex); congenital internal hydrocephalus; absence of diploë; slight aortic sclerosis; apical scar of left lung; edema and congestion of posterior parts of lungs; cholelithiasis.

Cultures from the left middle ear show Streptococcus pyogenes; from the right lung, Staphylococcus pyogenes aureus and a diphtheroid organism.

MICROSCOPIC EXAMINATION.

Heart.—One fasciculus shows a slight amount of fibrous replacement.

Lung.—Acute purulent bronchitis of the smaller divisions and bronchopneumonia. Little fibrin. The leucocytes are frequently phagocytic for pairs of cocci both flattened and lanceolate. Section from left apex shows dense fibrous tissue with lymph spaces containing granular material.

Spleen.—Engorged with blood. Pigmented cells frequent.

Liver.—Central cell columns narrowed, eosinophilic, in places pigmented. Central sinusoids injected. Pericellular spaces everywhere distinct and filled with granular coagulum. Characteristic picture of central atrophy with anilin blue stain. Considerable coarse vacuolation everywhere.

Pancreas.—Normal.

Adrenal.—Large collection of cells of the lymphocyte series. Numerous hyaline eosinophilic cells in adjacent columns.

Kidney.—Negative.

Testes.—Functionating slightly.

Thyroid.—Negative.

Parathyroid.—Fat-cells in central part. A few granular eosinophilic cells.

Hypophysis.—Large interlobular cysts. Large areas of fusiform green-pigmented cells in nerve portion. High proportion of eosinophilic cells in gland portion.

Material was taken from the right hemisphere for examination after various fixatives.

The left hemisphere was preserved entire in 10 per cent formalin and the following description and measurements are taken from it.

MEASUREMENTS.

Hemisphere.—From frontal to occipital pole, 21 cm.; from temporal to occipital pole, 16 cm.; from highest point of vertex to lowest point of temporal lobe, 13 cm.; from median fissure to most prominent part of parietal lobe, 7 cm.

Lateral Ventricle.—Antero-posterior diameter, 19.5 cm.; vertical diameter over corpus striatum, 6.5 cm.; vertical diameter from bottom of temporal horn, 12 cm.

Lateral Diameter.—Mesial, 4 cm.; occipital, 5 cm.; frontal, 4 cm.

The more prominent fissures show on the internal surface as fairly definite ridges on the ventricular wall.

The interventricular communication is oval in outline with an antero-posterior diameter of 7 cm. and a vertical diameter of 5 cm.

The corpus callosum is stretched out as a thin band around this opening, having a length of 19 cm. from the anterior commissure to the lower border of the splenius. In thickness it varies considerably. The anterior and recurved portions and the anterior half of the superior part average 2 mm., while the remainder measures 1 mm. back as far as the splenius, which is about 2 mm. thick.

FISSURES AND SULCI.

The Sylvian Fissure, from the origin of its anterior branches (common trunk) to the posterior ascending ramus, measures 75 mm. The two anterior branches arise as a common trunk 4 mm. in length. The anterior ascending ramus passes upward from here 20 mm. The horizontal branch, after leaving the common trunk, passes forward 7 mm. and divides into short perpendicular arms. The superior arm runs upward and forward for 9 mm. to end on the third frontal gyrus. The lower arm passes downward 4 mm. over a superficial annectant and runs into one of the smaller fissures of the prefrontal region.

Posteriorly the Sylvian fissure bifurcates into an ascending and a descending limb (Fig. 1 *Sa* and *Sd*). The ascending branch runs upward and backward 13 mm., then turns forward at a right angle for a distance of 3 mm., then upward and backward through a curve of short radius for a distance of 10 mm., ending by a transverse branch each limb of which is 5 mm. in length. This sulcus (Fig. 1 *Sa*) is very shallow, barely indenting the gyri into which it runs. The descending branch (Fig. 1 *Sd*) runs downward for 5 mm., where it sends off two branches, an anterior passing downward 3 mm. into the superior temporal convolution and a posterior running backward parallel to the course of the major portion of the Sylvian for a distance of 12 mm., where it is interrupted by a narrow deep-set annectant between the adjacent parietal and temporal convolutions. Superficially the sulcus passes over the annectant, which is hidden by the surrounding gyri so that the fissure apparently fuses with the superior temporal sulcus.

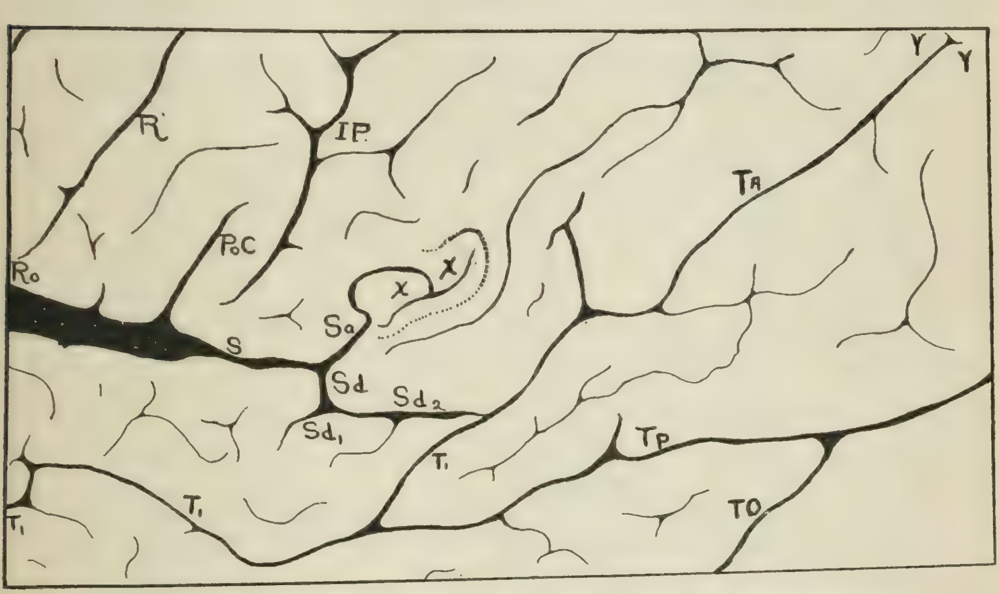


FIG. 1.—Projection outline of gyri and sulci. Sylvian region.

There is a fissure 8 mm. in length and of fair depth beginning in the fissure of Sylvius and indenting the precentral convolution just anterior to the Rolandic operculum.

The Rolandic Fissure (Figs. 1 and 2 *R*) is 11.2 cm. in length and makes an angle of 65° with the great longitudinal fissure. It extends on to the mesial surface for 5 mm. and is separated from the Sylvian fissure by an opercular gyrus 4 mm. in thickness. On spreading apart the borders of the fissure the lower parts of the precentral convolutions are seen to bulge into the space, encroaching on the postcentral. The site of the genu (Fig. 2 *Rg*) is marked by a short tributary sulcus 60 mm. below the mesial border, but the "great annectant buttress" of Campbell shows only as a low narrow ridge on the floor of the fissure.

The Precentral Sulcus is divided into a superior, median and inferior part.

The superior begins as a shallow groove on the mesial surface. On the lateral face it forms a tripartite figure each arm of which is about 10 mm. in length. The upper arm runs parallel to the central sulcus, the anterior passes forward parallel to the median fissure, while the third or descending ramus runs downward, curving slightly backward toward the Rolandic fissure.

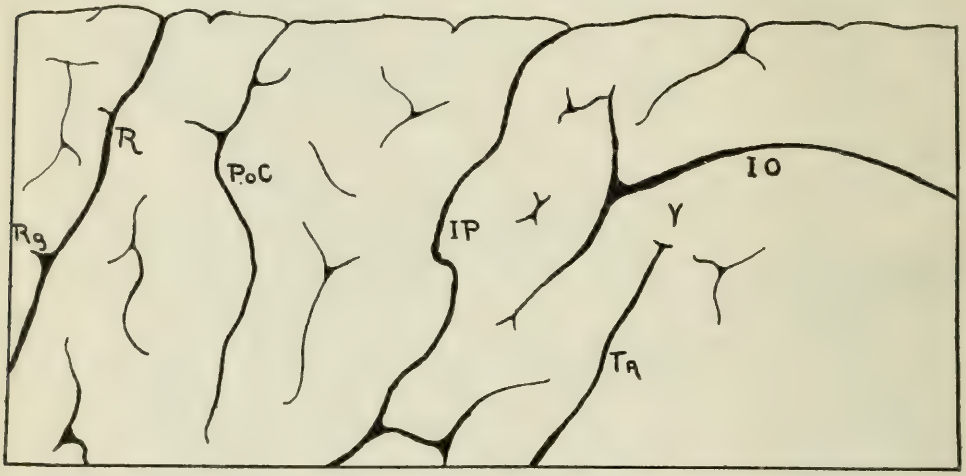


FIG. 2.—Projection outline of gyri and sulci. Postcentral region.

The middle portion shows again three divergent arms. The upper arm begins just below the middle of the anterior arm of the superior portion, with which it has a shallow communication (probably a vascular groove and not a true sulcus), and runs downward roughly parallel to the fissure of Rolando for 18 mm., from which point the other two branches arise. The posterior branch passes backward and downward 23 mm. parallel to the posterior branch of the superior portion. The anterior runs forward and slightly downward, then bends slightly upward for 12 mm., where it ends in a shallow short perpendicular sulcus.

The inferior part begins 5 mm. below the point of junction of the three branches of the middle portion, runs downward, converging slightly toward the Rolandic fissure, for 25 mm., where it divides into two arms. The posterior arm—ramus sagittalis posterior—runs directly backward for 10 mm. to within 4 mm. of the central fissure.

The anterior or inferior arm passes downward and slightly forward for 7 mm., where it gives off a descending branch 20 mm. in length and bends forward at almost a right angle for 11 mm., then turns downward again for 15 mm., then backward and slightly downward, where, after receiving a short tributary, it again bends to run parallel to the fissure of Rolando, reaching the Sylvian fissure, into which it opens by a shallow channel over a narrow gyrus. A large branch arises from the forward bend of this sulcus and is continued forward as the medial frontal.

The Frontal Sulci are indefinite, owing to their shallowness, their ramifications and the flattening and broadening of the gyri and annectants.

The Sulcus Frontalis Medius is the most prominent; arising, as above noted, from the anterior arm of the inferior portion of the precentral, it runs forward and toward the mesial border for 35 mm., where it gives off a large branch which joins the ramifications of the superior frontal sulci. Here it is deflected downward for 7 mm., then continues forward for 25 mm. to its end.

The superior frontal sulcus is represented by a tangled maze of fairly deep, frequently interrupted, anastomosing sulci.

The Fronto-marginal Sulcus (Wernicke) shows two divisions. The posterior portion begins in the fossa of Sylvius and passes forward as a very shallow groove for 15 mm., where it bends slightly toward the lateral surface, deepens and becomes somewhat tortuous, continuing for 35 mm. to its terminus. At two points near its anterior end it is separated from the anterior portion by very narrow intervening gyri. The anterior part is a fairly deep, slightly wavy sulcus 27 mm. long running to a point within 4 mm. of the mesial border.

ORBITAL SURFACE.

The Olfactory Sulcus is 40 mm. long. At its posterior extremity it lies 13 mm. distant from the median fissure; but as it passes forward it gradually converges and finally passes over on to the mesial surface, so that the last cm. is not visible from below.

The posterior arms of both the median and lateral orbital sulci and the sulcus cruciatus are well developed. The anterior arm of the median is 15 mm. long and ends in a sulcus bordering the first of three narrow convolutions grouped at the frontal pole, with their long axes roughly perpendicular to the longitudinal fissure. The anterior arm of the lateral sulcus is lost after a short distance in a tangle of shallow sulci running in a general way parallel to the fronto-marginal sulcus.

PARIETAL LOBE.

Postcentral.—The superior part of the postcentral sulcus is a continuation of the sulcus cinguli and extends on to the lateral surface as a deep incisure for 35 mm., diverging slightly from the Rolandic fissure.

The inferior portion of the postcentral is a cleft 20 mm. long beginning in the fissure of Sylvius 15 mm. behind the fissure of Rolando and parallel to the latter. No mesial portion is present, its place being taken by a diversion of the interparietal.

Interparietal (proprius) begins 5 mm. above Sylvian fissure and 20 mm. behind the fissure of Rolando. It runs upward in a curve of large radius, convex forward, for 53 mm., dividing into an anterior and a posterior branch. At the summit of the convexity it comes to within 10 mm. of the fissure of Rolando, to which it sends a deep collateral. The anterior branch runs forward and upward and ends on the superior part of the postcentral gyrus after a course of 10 mm. The posterior branch passes backward for 40 mm. parallel to the median fissure. Midway in its course it gives off an ascending branch (parietalis transversus) which runs parallel to the central fissure to reach the mesial surface, on which it descends 5 mm., then turns back at a right angle and continues for 15 mm. The posterior branch also gives off a shallow descending ramus at a point 7 mm. behind the origin of the transverse parietal. This branch passes downward for 20 mm., then bends backward to join an extension of the superior temporal sulcus described below. There is a deep sulcus beginning 5 mm. from the mesial border and running down roughly parallel to the transverse parietal for 25 mm., representing the stipe and ramus of origin of the interoccipital (Wilder). From its mid-portion it gives origin to a perpendicular sulcus which runs backward over the occipital lobe for 6 cm., growing shallower as it progresses until it finally runs out into a shallow vascular groove. This sulcus is probably the homologue of the interoccipital (Fig. 2 *IO*) but is not continuous with the interparietal.

TEMPORAL LOBE.

Superior Temporal Sulcus (Fig. 1 T_1) begins on the lateral aspect a little behind the temporal pole and opposite the origin of the common trunk of the anterior ascending and horizontal rami of the fissure of Sylvius and runs backward parallel to the latter and about 5 mm. from it for 35 mm. Here it is offset by a superficial annectant to a position 2 mm. lower on the lateral surface, in which plane it continues for 15 mm., then returns to its original level and passes backward in an elongated S shape for 35 mm., where it divides into a superior or ascending and an inferior or posterior branch.

The superior or ascending arm (Figs. 1 and 2 *TA*) passes upward and backward roughly parallel to the Rolandic fissure for 90 mm., ending on the gyrus which forms the inferior boundary of the interoccipital sulcus. As it passes the end of the descending branch of the fissure of Sylvius it receives a superficial continuation therefrom. Its deeper portion is, however, distinct, owing to the interposition of a deep annectant between the superior temporal and parietal convolutions.

The posterior branch of the first temporal (Fig. 1 *TP*) passes backward in the general direction of the main trunk of the first temporal for 70 mm., ending on the flattened occipital lobe.

The Second Temporal Sulcus is represented anteriorly by short, shallow, irregular clefts with no definite arrangement.

The Third Temporal Sulcus probably has its homologue in a cleft 40 mm. in length running forward and inward from the temporo-occipital angle.

Arising from the tangle of sulci at the temporo-occipital angle is a deep sulcus 50 mm. in length running upward and slightly backward and terminating in the posterior branch of the first temporal. This sulcus is probably the occipito-temporal of Lussana and gains in interest when the distribution of the cortex is considered. Its upper extremity (*TO*) and its anastomosis with the first temporal are shown in Fig. 1.

Except for these sulci the inferior surface and temporal pole are marked only by branching vascular grooves and show no division into gyri. One of these vascular grooves takes the position of the fissura rhinica and will be mentioned later in the description of the distribution of the pyriform lobule.

OCCIPITAL LOBE.

Except for the sulci described above as continuations of the parietal and temporal sulci the lateral surface of the occipital lobe shows no sulci.

The Lateral Occipital is 2 cm. in length and runs along the inferior margin of the lobe.

The Fissura Collateralis begins at a point on the inferior surface of the temporal lobe about 15 mm. behind the level of the posterior border of the crus cerebri and passes backward 35 mm., then deviates upward for a short curve, again resuming its original direction to end in the lateral occipital after a total course of 95 mm. Near the crest of its deviation it sends two short rami on to the mesial surface. The anterior of these two sends a branch forward to the anterior part of the common trunk of the calcarine and parieto-occipital.

MESIAL ASPECT.

The Sulcus Cinguli.—The anterior part begins at the "carrefour" of Broca and runs closely parallel to the corpus callosum for 9 cm., then gradually rises toward the superior margin, where it runs out on the mesial surface of one of the frontal gyri. Two cm. before its terminus it gives off a branch passing diagonally backward and downward to the median part, which begins opposite the point where the anterior portion diverges from the line parallel to the corpus callosum and runs backward to outline the paracentral lobule, where it turns upward, crossing the superior border, and becomes the superior part of the postcentral sulcus. The median division of the sulcus cinguli sends a branch downward and backward, just before it turns to enclose the paracentral lobule, for a distance of 15 mm. This probably represents the posterior part of the sulcus cinguli.

The Sulcus Rostralis begins 3 mm. downward and forward from the point of origin of the anterior part of the sulcus cinguli and follows the latter closely at a distance of about 5 mm. with only one interruption for 9 cm. It sends several short rami forward, all of which end at or near the margin of the mesial surface.

The Paracentral Sulcus begins on the superior border of the precentral convolution, passes downward 10 mm., then turns sharply backward for 15 mm., ending within 5 mm. of the median part of the sulcus cinguli.

The Sulci Precunei are represented by one deep sulcus 35 mm. long and several shallow short branches.

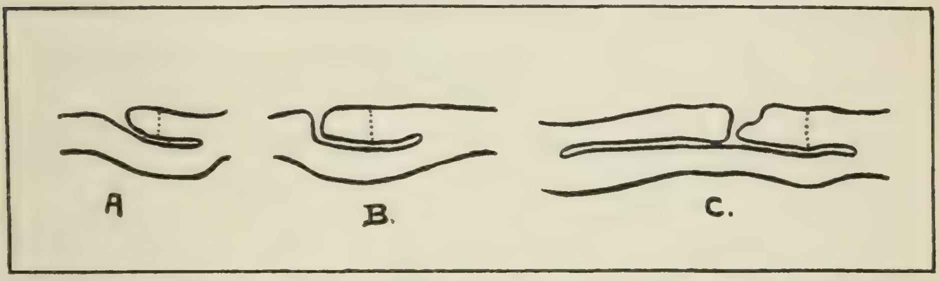


Fig. 3.—Diagram to illustrate angles of sulcal penetration.

The Common Trunk of the *Calcarine* and *Parieto-occipital* fissures (sulcus calcarinus proprius of Elliot Smith) arises in the plane of the splenium of the corpus callosum and passes backward and upward for 30 mm. to its division.

The Calcarine Fissure runs backward and downward for 70 mm., ending near the inferior border of the mesial aspect of the occipital pole in a transversely placed sulcus 8 mm. in length, the fissura extrema of Seitz or retrocalcarine fissure of Monakow.

The depth of the various fissures is more or less misleading, owing to the frequent occurrence of oblique direction of penetration (Fig. 3 *A*) or to angulation of their downward course. In many instances a sulcus passes directly inward only a few millimeters, then turns at an abrupt angle and continues parallel with the surface for some distance (Fig. 3 *B*). In other cases the lower or parallel portion passes in both directions from the vertical trunk (Fig. 3 *C*). This latter condition seems generally dependent on the presence of two adjacent annectant buttresses, each encroaching on the opposite convolution and thus turning the parallel portion of the sulcus first in one direction and then the other, the line of section afterward passing through both arms. In a few instances, however, this double-angled figure is observable where such an explanation is not tenable.

The average depth of the main fissures and sulci has been measured, including both arms of the angle in such instances as Fig. 3 *C*. The appended table gives the depth in two columns, *i. e.,* the oblique or total penetration and the direct or actual distance from the top of the adjoining convolution to the deepest point reached by any part of the sulcus (Fig. 3, dotted lines). The first column is left vacant in those fissures whose direction is normal.

Fissure or Sulcus.	Average oblique penetration.	Average direct depth.
Sylvian. Mid-portion of posterior limb		To top of insular convolutions.. 1.75 mm. To bottom of insular sulci.... 2.5 mm.
Rolando	15 mm.	7 mm.
Precentral	8 mm.	5 mm.
Postcentral	7 mm.	5 mm.
Midfrontal	......	5 mm.
Cinguli.		
Anterior branch	5 mm.	4 mm.
Median branch	15 mm.	5 mm.
Calcarine	10 mm.	2 mm.
Parieto-occipital	7 mm.	2 mm.
Interparietal	10 mm.	5 mm.
Interoccipital	10 mm.	1 mm.
Superior temporal	......	10 mm.

THICKNESS OF BRAIN WALLS.

Plate II shows in general the relation of the size of the ventricular cavities to the walls.

The table below gives the average and maximal and minimal thickness of the walls in the various surfaces and borders of the different lobes.

Lobe.	Surface or Border.	Average thickness.	Maximal thickness.	Minimal thickness.
Frontal	Lateral surface	11 mm.	14 mm.	9 mm.
	Mesial surface	10 mm.	13 mm.	7 mm.
	Orbital surface	10 mm.	15 mm.	9 mm.
	Superior border	19 mm.	20 mm.	17 mm.
	Inferior border	20 mm.	25 mm.	18 mm.
Parietal	Lateral surface	20 mm.	25 mm.	1 mm.
	Mesial surface	5 mm.	6 mm.	4 mm.
	Inferior surface:			
	Corpus striatum	30 mm.	35 mm.	20 mm.
	Superior border	15 mm.	20 mm.	10 mm.
Temporal	Lateral surface	5 mm.	10 mm.	4 mm.
	Mesial surface	2 mm.	2 mm.	2 mm.
	Inferior surface	3 mm.	5 mm.	1 mm.
Occipital	Lateral surface	5 mm.	7 mm.	2 mm.
	Mesial surface	5 mm.	7 mm.	3 mm.
	Inferior surface	6 mm.	8 mm.	2 mm.

Plate II shows a series of sixteen sections, averaging 13 mm. in thickness, through the left hemisphere. The corpus striatum first appears about the middle of the fourth section, *i. e.*, approximately 45 mm. from the frontal pole. The usual relation of the caudate and lenticular nuclei is observed. At the beginning of the fifth section the corpus striatum is 13 mm. in thickness. The major part is made up of caudate nucleus, which is separated from the lenticular by a line of isolated bundles representing the first view of the internal capsule.

The sixth section (Fig. 4) shows a well-defined internal capsule. The total width of the corpus striatum here is 20 mm., of which 12 mm. is lenticular nucleus, 4 mm. is caudate nucleus, the remaining 4 mm. being occupied by the capsule. The caudate has moved slightly upward and outward. The optic thalamus begins about the middle of this section and runs to the middle of the next.

In the seventh section the lenticular nucleus has disappeared and the caudate is represented by an elongated patch 1 mm. thick by 5 mm. long above the thalamus, which is 10 mm. in greatest width. This section includes the corpora mammillaria and most of the crus cerebri.

The next section (No. 8) contains the hinder part of the crus and passes through the communication into the temporal horn of the ventricle.

The island of Reil is first seen in the third section and continues back as far as the ninth. It is considerably flattened but through it is the thickest amount of cerebral substance.

GYRI.

In general it may be said that the gyral width is proportionate to the degree of attenuation of the cerebral wall. Thus the prefrontal and orbital gyri are of approximately normal width. Such gyri as are outlined on the occipital and temporal lobes are considerably widened, while the lateral convolutions show variations following roughly the same rule. Those which pass up over the mesial border, *e. g.*, the pre- and postcentrals, are broader on the convex surface and narrow as they approach the thicker portions near the border.

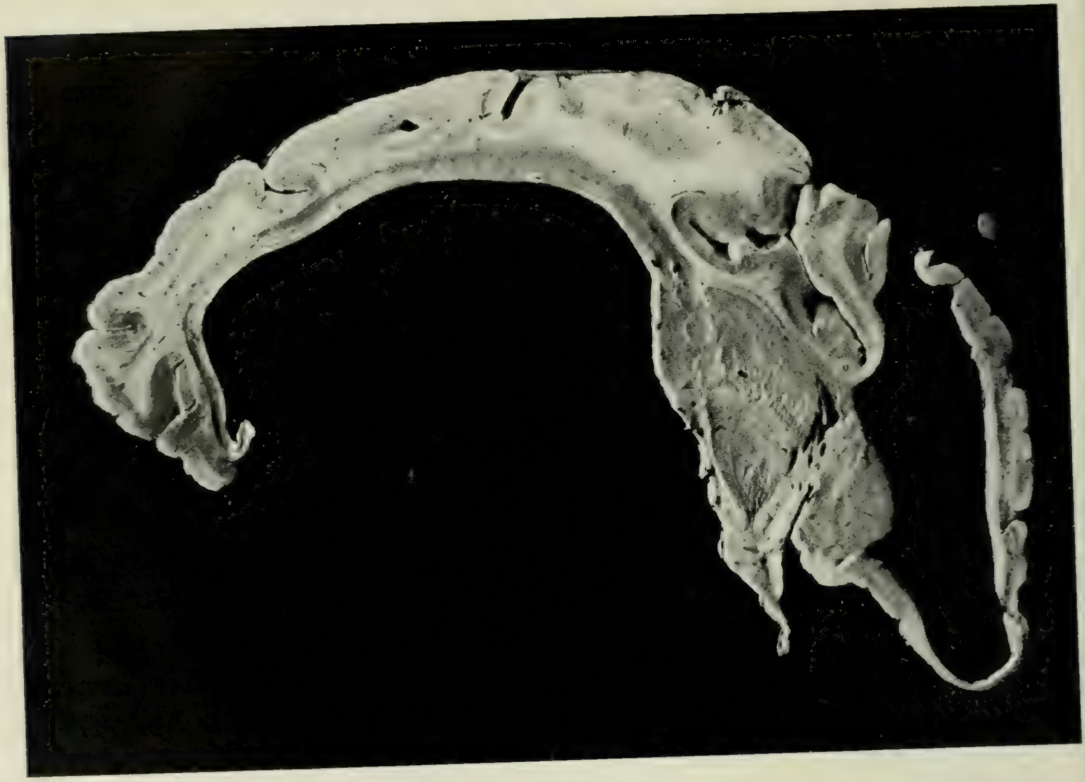


FIG. 4.—Photograph of Section 6, Plate II.

The precentral convolution reaches a width of 25 mm. in places, while the postcentral is proportionately wide. On the mesial surface the continuations of these gyri forming the paracentral lobule are considerably less broad, averaging 10 mm.

The limbic lobe is about 10 mm. in width anteriorly, broadening to 15 mm. as it passes backward.

In many places the wider convolutions show a tendency toward the formation of superficial indentations or abortive sulci, to which Wilder has applied the name fossulæ. These show, however, on microscopic examination, merely as depressions, and not as true divisions of the cortical matter, as do some of the vascular grooves of the occipital and temporal lobes which will be described later.

The two limbs *XX* at the end of the posterior ascending limb of the fissure of Sylvius (Fig. 1) are very shallow, and the portion outlined by dotted lines may be taken to represent the supramarginal convolution.

Figs. 1 and 2 *Y* represent the angular gyrus, which in this instance is high on the convexity.

The superior temporal gyrus is narrow anteriorly, broadening as it passes backward, a condition which is explained by the prolongation into it of a widened ventricular cleft (Fig. 6) and which proves of interest in connection with the distribution of the audito-sensory type of cortex.

On opening the fourth ventricle it is seen to be of about normal size. Its ependyma is smooth but on section appears irregularly thickened. The aqueduct of Sylvius is entirely obliterated as far as can be seen by gross examination, at about its mid-portion, by a firm partition crossing it at right angles to its long axis. Behind this obstruction the canal is of about its usual diameter, while in front its walls diverge sharply to open into the widely dilated third ventricle. Sections of this partition stained by Mallory's original neuroglia method (mordanting in ammonium bichromate and picric acid and staining with phosphotungstic acid hematein after formaldehyde fixation) show it to be made up entirely of close-meshed neuroglia network containing many glia cells, some of which are multinucleated, and several small canals lined with cuboidal ependyma-like cells, some of which show cilia. Serial sections were cut from a paraffin block of that portion of this area lying to one side of the median line and the course of all of these canals traced. The majority of them passed in short distances to end blindly, but a few, and in every instance these were the wider ones, opened out both ways—anteriorly into the aqueduct in front of the obstruction and posteriorly into the fourth ventricle, thus forming a direct channel of communication past the obliterating partition.

The surrounding tissues near the lesion show a well marked neuroglia increase. The choroid plexus of the fourth ventricle is normal. The foramina of Magendie and of Key and Retzius are patent. The cerebellum is normal both to gross and microscopic examination. Sections of the cord from the fourth cervical, second dorsal, third lumbar and first sacral regions, stained by the Nissl, Weigert and phosphotungstic acid hematein methods for the display of the cells, fibers and neuroglia, show no abnormalities except an occasional eccentric nucleus in an anterior horn cell.

The anterior choroid plexuses show many concentrically layered hyaline bodies and few villi.

The cells of the caudate and lenticular nuclei are normal in morphology and distribution.

The microscopic examination of the cerebral cortex will be taken up in detail but a general description is here included. The cortical picture from all regions is one of intense cell richness. This is more marked in the areas where the distension has been most active, *i. e.,* where the wall is thinnest, but is evident enough to be noticeable at first glance everywhere. The pia over the frontal cortex in the region of the exudate mentioned in the gross description shows numerous polymorphonuclear leucocytes and also many large mononuclear cells, some of which are phagocytic for the leucocytes. Neuroglial reaction beneath the pia is evidenced by swollen cell bodies and multiple nuclei.

Phosphotungstic acid hematein stains of various cortical areas show a diffuse fine fibrillar neuroglia meshwork of fairly uniform distribution but in general thicker beneath the pia and at the bottom of the sulci. In some areas the gliosis is quite marked but these will be mentioned in the later description of the cortex.

The ependyma of the lateral and third ventricles is everywhere smooth and shows no nodular glial elevations. The ependymal lining consists of flattened cells very few of which show cilia.

At many places beneath the ependyma are collections of small hyaline globules in irregular clusters or lined up along the blood-vessels.

In order to determine more definitely the cell changes and fiber variations of the different types of cortex and to outline the distribution of the various fields, sections were taken from the various border line areas and from the centers of fields of the left hemicerebrum and compared with Campbell's charts and descriptions. The cell studies were made after celloidin embedding (20-micron sections) and staining in $\frac{1}{4}$ of 1 per cent aqueous solution of thionin. The fibers were stained by the Weigert process in 30-micron celloidin sections. Phosphotungstic acid hematein stain was used for neuroglia in places where changes were indicated.

No attempt was made to section the entire cerebral cortex, but sections were taken from the centers of the fields to serve for a description of types and other blocks were cut along the border lines or boundaries of the normal distribution of cortical variations. In some instances these had to be supplemented by additional pieces, but by this method a fairly accurate outline of the distribution was reached and oblique sections were more readily avoided. Occasionally one block was cut long enough to show three types but as a rule they served to overlap the junction of two only. In this way 224 blocks sufficed to limit the fields.

In the following account of the cell lamination and fiber arrangement Campbell's descriptions and classification have been closely followed though reference has also been had to the work of S. Ramón y Cajal, Hammarberg, Kaes and others. In comparing cell sizes in various areas, *viz.,* the Betz cells as compared with the large pyramidals of the postcentral convolutions, the camera lucida has been employed. At first numerous cells from each field were drawn and the drawings compared; but a more rapid and easier method was finally adopted, *i. e.,* that of drawing a number of typical cells of one area on a sheet of paper and then superimposing, at the same magnification, the image of the cells in another zone onto the copied outline of the first. The outline can be heavily inked and the work of comparison of size and shape is thus greatly facilitated.

PRECENTRAL CORTEX.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Contains fibers of the small and large varicose and evenly medullated medium-sized types in that order of frequency, the last-named being rather few in number.

2. *Supraradiary Field.*—Rich network of fine fibrils. No larger fibers found.

3. *Line of Baillarger.*—Not very definite. There are many fine fibrils and a few coarser ones in this position, but they can scarcely be said to form a definite line and they fuse below with the interradiary plexus.

4. *Radiations of Meynert.*—These bundles are very strong. They show from one to three large varicose fibrils and an occasional evenly medullated fiber of large size in a dense bundle of fine fibers. The radiations pierce the position of the line of Baillarger and enter the supraradiary field.

5. *Interradiary Plexus.*—Rich network of fine varicose fibrils.

6. *Association Fibers.*—Large transverse and oblique fibers well represented.

CELL LAMINATION.

1. *Plexiform Layer.*—This layer is thick in the motor cortex and its width serves as one of the differentiating points from the surrounding types. It contains many small round and oval cells and occasionally one of the fusiform shape with its long axis parallel to the gyral surface.

2 and 3. *Layers of Small and Medium-Sized Pyramidal Cells.*—These lamina can not be separated into their two parts. The layer consists of intermingled cells of the two sizes, only about one-half of which show differentiation into a pyramidal form.

4. *External Layer of Large Pyramidal Cells.*—Distinct lamina. Cells large and show an abundance of chromophilic particles. Some are pyknotic.

5. *Layer of Stellate Cells.*—Irregular in width but recognizable everywhere. Few small pyramidals scattered among the stellates.

6. *Internal Layer of Large Pyramidal Cells.*—The large pyramidals of this layer are not so large as those of the external layer. The Betz cells are typical as regards size, morphology and position, except that an occasional cell conforming to the Betz type is found in or even above the stellate layer. Some of the Betz cells are pyknotic.

7. *Layer of Fusiform Cells.*—Fairly deep and contains many spindle-shaped and small pyramidal cells and about an equal number of undifferentiated cells.

DISTRIBUTION.

Mesial Surface.—The anterior and lower borders of the motor cortex on the mesial surface are marked sharply by the paracentral sulcus. The posterior border is roughly speaking a line drawn from the mesial end of the fissure of Rolando to the lower end of the paracentral sulcus.

Lateral Surface.—The fissure of Rolando serves to define the motor area posteriorly. The oblique direction of penetration is followed closely by the cortical distribution. Thus the change from precentral to postcentral type can be made out as taking place at the bottom of the fissure, which is in some places 5 to 10 mm. behind its position on the surface, the motor type underlying the sulcus with cortex of postcentral structure above it. The annectant buttress at the level of the genu shows a structure which places it in the motor field but its differentiation is imperfect and parallels its anatomical development. It contains a very few cells towards its anterior end which may be regarded as Betz cells.

The anterior boundary of the precentral area is followed with difficulty. At the mesial border it is limited by the paracentral sulcus and from here it widens out forward covering three-fourths of the precentral gyrus along the distribution of the superior division of the precentral sulcus. Along the length of the superior ramus of the middle division it covers half of the field between the latter and the fissure of Rolando, continuing as a belt of about even width enveloping the ramus sagittalis posterior and reaching forward to the anterior branch of the first bifurcation of the inferior division of the .sulcus precentralis and its descending branch. From this point the breadth of the motor " skirt " diminishes rapidly, ending about 8 mm. above the lower end of the fissure of Rolando.

POSTCENTRAL CORTEX.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Fewer fibers of all types, and notably of the larger sizes, than the precentral. The layer is also considerably narrower than that covering the motor field.

2. *Supraradiary Zone.*—Fairly rich tangle of fine fibers. Occasionally a horizontal varicose fiber of medium size.

3. *Line of Baillarger.*—Poorly represented. Fine fibrils running in all directions.

4. *Radiations of Meynert.*—Not so strong as in the precentral area. Made up chiefly of small fibers and only a few very large ones.

5. *Interradiary Plexus.*—Rich but markedly less so than in precentral.

6. *Association Fibers.*—Many and large and running in all directions, though chiefly horizontally.

CELL LAMINATION.

1. *Plexiform.*—Cell content less rich than in precentral cortex but of much the same type.

2. *Layer of Small Pyramidal Cells.*—Thick closely packed layer of small cells, not more than one in twenty of which shows a pyramidal form.

3. *Layer of Medium-Sized Pyramidal Cells.*—Cells better differentiated.

4. *External Layer of Large Pyramidal Cells.*—Many large cells but appreciably smaller by camera-lucida comparison than the homologous cells of the motor cortex. Numerous smaller pyramidals scattered through this layer.

5. *Layer of Stellate Cells.*—Wide and thickly packed with poorly differentiated cells.

6. *Internal Layer of Large Pyramidal Cells.*—Many giant cells, but measurably smaller than the Betz cells. Many large pyramidals.

7. *Layer of Fusiform Cells.*—Layer fairly deep. Much like precentral in type.

DISTRIBUTION.

Mesial Surface.—On the paracentral lobule the postcentral type of cortex forms a rough parallelogram about 6 mm. wide, limited anteriorly by the line given above as the posterior boundary of the precentral type.

Lateral Surface.—Here the cortex bearing this structure forms a gradually narrowing band, occupying approximately half of the postcentral gyrus and ending about 10 mm. above the lowest point reached by the motor type.

Visuosensory or Calcarine Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Rather narrow. Numerous small varicose fibrils. Few evenly medullated medium-sized fibers. No coarse varicose.

2. *Supraradiary Layer.*—Rich network of fine varicose fibrils. The radiations of Meynert extend into this field as quite prominent bundles.

3. *Line of Gennari (or Vicq d'Azyr)* is an exceedingly rich band of longitudinally placed fine fibrils through which can be plainly seen the thick radiary bundles.

4. *Radiations of Meynert.*—Thick groups of fibers in which the fine varicose type predominates. The large evenly medullated fibers are numerous. Coarse varicose fibers are rather few.

5. *Interradiary Plexus.*—Well developed and consisting of numerous fine fibrils of a fairly uniform size throughout. No definite pallid lamina can be made out beneath the line of Gennari.

6. *Association Fibers.*—Many horizontal evenly medullated fibers of large caliber.

CELL LAMINATION.

1. *Plexiform Layer.*—Contains practically no differentiated cells. Chiefly oval nuclei with no protoplasm.

2. *Layer of Small Pyramidal Cells.*—Cells imperfectly developed. Not more than one cell out of a dozen shows a pyramidal outline. For the most part they are small oval nuclei, with little or no protoplasm.

3. *Layer of Medium-Sized Pyramidal Cells.*—Shows considerably better differentiation than last layer.

4. *Layer of Large Stellate Cells.*—Fairly numerous and typical.

5. *Layer of Small Stellate Cells.*—Close-packed and fairly well differentiated.

6. *Layer of Small Pyramidal Cells with an Ascending Axis-Cylinder.*—Few and with difficulty separated from lower layer.

7. *Layer of Giant Pyramidal Cells (Solitary Cells of Meynert).*—Few in number but typical in morphology. Rarely more than one in a low-power field.

8. *Layer of Medium-Sized Pyramidal Cells.*—Fairly numerous and well developed.

9. *Layer of Fusiform Cells.*—Numerous fusiform and a few triangular cells. Almost all lie with their long axes parallel to the ventricular surface.

DISTRIBUTION.

The calcarine type of cortex begins as a narrow band beneath the stem of the calcarine and parieto-occipital fissures (the calcarinus proprius of Elliot Smith), and passes backward in a widening band without crossing the fissure, except by the underfolding due to the oblique penetration, as far as its point of division. Along this common trunk is one of the places where a double deflection of the bottom of the fissure has occurred (Fig. 3 *C*), and the calcarine type of cortex is here found to envelop one arm completely and end opposite the bottom of the second, thus seemingly indicating the latter as the original sulcal fundus. At the point of origin of the calcarine and parieto-occipital fissures the visuosensory cortex crosses the former and its upper border runs backward and slightly downward to within 10 mm. of the occipital pole, where it turns sharply downward to and around the inferior margin. The scarcity of sulci on this surface renders difficult a descriptive outline, but in general the field may be said to have a rough pyriform shape with its narrow end bent slightly downward to conform to the course of the calcarine stem. Its lower portion passes the inferior angle and appears as a small patch on the lateral surface, but on the inferior aspect instead of the pole, as Campbell plots it. This downward displacement of the field is probably the result of disproportionate distension of the overlying occipital and occipito-parietal portions.

Visuopsychic Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Many small varicose fibers. No fibers of larger caliber.

2. *Supraradiary Zone.*—Chiefly small fibers. Occasional coarse fiber extending up from the radiations. Numerous fibers, both

fine and course, are seen running transversely, but they are not compact enough to form a definite line of Kaes.

3. *Line of Baillarger.*—Poorly marked. In thick sections an indefinite, frequently interrupted wide band can be made out. Consists of a few medium-sized varicose fibers and many smaller ones. Upper and lower boundaries indefinite.

4. *Radiations of Meynert.*—Definite but not nearly so well marked as in the calcarine. Practically every radiation contains one, sometimes two, large varicose fibers, a bundle of small fibrils and an occasional evenly medullated medium-sized fiber.

5. *Interradiary Plexus.*—Many fine fibrils running in all directions.

6. *Association Fibers.*—Numerous. Coarse fibers chiefly horizontal or slightly oblique in direction.

CELL LAMINATION.

1. *Plexiform Layer.*—Very much like visuosensory cortex except that the layer is much thicker.

2. *Layer of Small Pyramidal Cells.*—Very much like the same layer in the calcarine cortex.

3. *Layer of Medium-Sized Pyramidal Cells.*—The layer is better differentiated. The pyramidal contours and the beginning of basal processes can be made out in fully half of the cells.

4. *External Layer of Large Pyramidal Cells.*—Well shown. Many cells of fairly large size with well developed basal processes. Some of the larger show a few small chromophilic particles. Some are pyknotic. The sharp demarcation of this layer of cells serves to distinguish this type of cortex from the calcarine very readily in sections stained for the cells. In the fiber preparations the broad line of Baillarger answers equally well and the two are found to be very exactly coincident.

5. *Layer of Stellate Cells.*—This layer is very much like the second stellate layer of the calcarine zone.

6. *Internal Layer of Large Pyramidal Cells.*—Fairly well shown. Cells not so large as those of the external lamina and interspersed with many small pyramidals. Near the border of the visuosensory cortex an occasional solitary giant cell is found in cortex which otherwise bears visuopsychic characteristics.

7. *Layer of Fusiform Cells.*—Not remarkable.

DISTRIBUTION.

Mesial Surface.—Below the calcarine cortex the visuopsychic type begins near the anterior end of the calcarine stem and passes backward as a band about 10 mm. wide, broadening to 20 mm. beneath the point of division of this fissure, again shrinking to 10 mm. as it turns downward to cross the lower boundary. In its course it comes in relation with the fissura collateralis and is in part limited by it. The anterior extension of this field beneath the calcarine stem could not be exactly determined on account of the very gradual transition here to the type of common temporal. This area is shown on the diagram by mixed short lines and dots. Above the calcarine field the visuopsychic type occupies the remainder of the cuneus.

Lateral Surface.—On this aspect the visuopsychic cortex covers all of the occipital pole except the small area described for the calcarine and extends as far forward as the sulcus which has been mentioned in the gross description as the occipito-temporal of Lussana. The demarcation of this field is very sharp along the sulcus and its relationship will be more fully discussed later.

AUDITO-SENSORY CORTEX.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Many fine varicose fibrils and fairly numerous large varicose fibers.

2. *Supraradiary Zone.*—Fiber content not rich. Chiefly small fibers. Some medium-sized varicose fibrils running in a horizontal direction which are numerous enough so that in sections of 30 microns or over a line of Kaes can be recognized.

3. *Line of Baillarger.*—A wide poorly demarcated zone of only slightly greater fiber wealth than the subjacent layer. Chiefly small varicose fibrils.

4. *Radiations of Meynert.*—Short, fairly thick bundles with numerous medium-sized varicose fibers and many small fibrils.

5. *Interradiary Plexus.*—Rich network of small fibrils.

6. *Association Fibers.*—Many large horizontal and oblique fibers.

CELL LAMINATION.

1. *Plexiform Layer.*—Contains an occasional small fusiform cell.

2 and 3. *Layers of Small and Medium-Sized Cells.*—These layers can not be separated. The variations in cell size are slight and they maintain no definite laminate assortment. The cells are rather poorly differentiated.

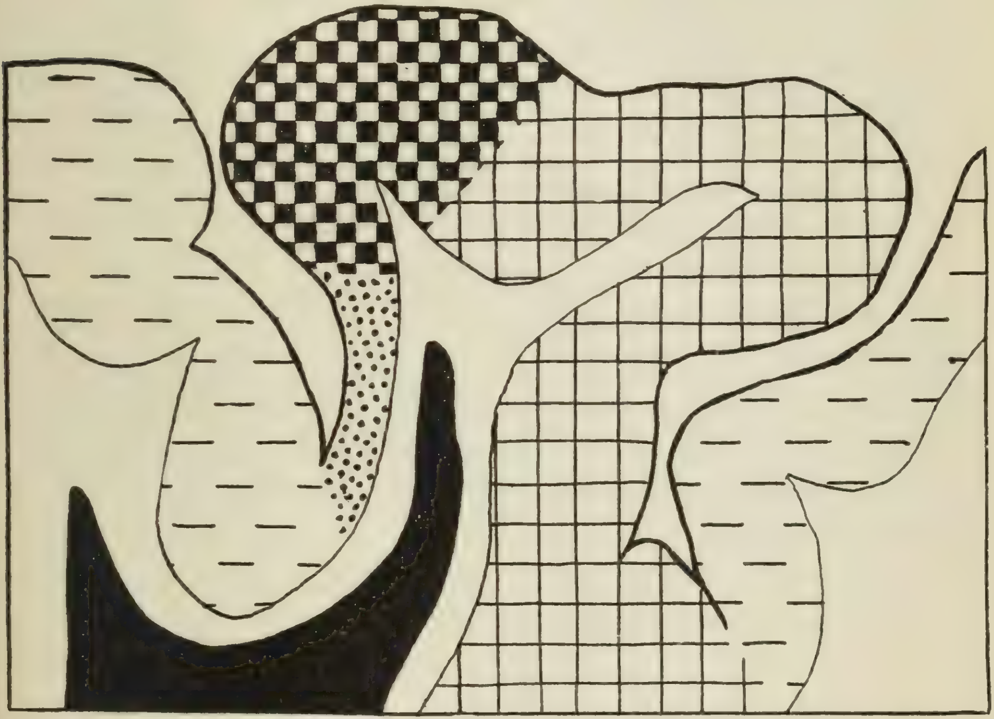


FIG. 5.—Diagram of cortical arrangement through the temporal horn of the lateral ventricle.

4. *External Layer of Large Pyramidal Cells.*—Very few undifferentiated cells. Giant cells numerous, usually two or three in each low-power field. Basal and apical processes strong. Chromophilic particles large and numerous. Some of these cells are pyknotic and their size is only slightly less than that of the Betz cells of the motor cortex.

5. *Layer of Stellate Cells.*—Narrow layer, rich in cells.

6. *Internal Layer of Large Pyramidal Cells.*—Many pyramidal cells of medium size but few large ones.

7. *Layer of Fusiform Cells.*—Fairly deep lamina. Many fusiform cells, the lower of which show a tendency to lie with their long axes parallel to the ventricular wall.

DISTRIBUTION.

The audito-sensory cortex has a distribution which calls for special explanation. Instead of being entirely concealed within the fissure of Sylvius and occupying its inferior wall as Campbell locates it, cortex which is undoubtedly of the audito-sensory type is found extending out on to the lateral surface of the superior temporal convolution for a distance, in places, of 10 mm. This is explained by a transverse section through the region (Fig. 5), which shows a narrow bay-like extension of the ventricular cavity. This cavity comes very close to the surface along the inferior Sylvian wall, and at this point the cortex shows a very low degree of differentiation and can not be classified. Above, on the superior surface of the first temporal gyrus, is audito-sensory cortex which has been turned out, as it were, from the Sylvian wall. Anteriorly this type of cortex is found as far forward as the opercle of the precentral gyrus, while posteriorly it extends to within 6 mm. of the point of bifurcation of the Sylvian.

Audito-Psychic.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Numerous small varicose fibrils.

2. *Supraradiary Zone.*—Few fine, irregularly placed varicose fibers. Few long evenly medullated fibers in a position to suggest a line of Kaes. Radial prolongations fairly definite.

3. *Line of Baillarger.*—Ill-defined. Fibers forming it are of the small varicose type and widely separated.

4. *Radiations of Meynert.*—Closely set but rather poor. Consist of a few medium-sized varicose fibers in a group of finer ones. Extend into supraradiary field.

5. *Interradiary Plexus.*—Markedly less prominent than in audito-sensory area.

6. *Association Fibers.*—Coarse horizontal fibers, few in number.

CELL LAMINATION.

1. *Plexiform Layer.*—Same as audito-sensory.

2 and 3. *Layer of Small and Intermediary Pyramidal Cells.*—Slightly more laminate assortment than in audito-sensory, but contains a less number of differentiated cells.

4. *External Layer of Large Pyramidal Cells.*—Giant cells scarce and measurably smaller than in foregoing type. Large pyramidals fairly numerous.

5. *Layer of Stellate Cells.*—About like audito-sensory area, but arranged in columns to accommodate the radiations.

6. *Internal Layer of Large Pyramidal Cells.*—Contains few large cells. Medium-sized pyramidals numerous. This layer is not well demarcated from that below.

7. *Layer of Fusiform Cells.*—Numerous and thickly packed.

DISTRIBUTION.

This type of cortex is found covering all of the first temporal convolution back of a point 10 mm. behind the junction of the precentral sulcus with the fissure of Sylvius, to the upturned end of the first temporal sulcus, except that occupied by audito-sensory. The deep annectant between the parietal convolutions and the first temporal, which really cuts off the fissure of Sylvius, is found to bear features common to both the audito-psychic and common temporal types, but should probably really be classed with the former.

Common Temporal.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Very few fine fibers. None of larger caliber.

2. *Supraradiary Zone.*—Outer layers have only a very few delicate fibers. Lower contain a very poor meshwork of fine fibers. No line of Kaes.

3. *Line of Baillarger.*—Few fine fibers with a horizontal direction. Scarcely recognizable.

4. *Radiations of Meynert.*—Poor. Chiefly fine fibrils. Only an occasional medium-sized fiber and no larger ones.

5. *Interradiary Plexus.*—Very few fine fibrils.

6. *Association Fibers.*—Sparse and small in size.

CELL LAMINATION.

1. *Plexiform Layer.*—Like other temporals, but less thick.

2 and 3. *Layer of Small and Medium-Sized Pyramidal Cells.*—Not separable. Very poor differentiation.

4. *External Layer of Large Pyramidal Cells.*—No giant cells. Large cells definitely smaller than audito-psychic and rather few in number.

5. *Layer of Stellate Cells.*—Narrow and ill-defined.

6. *Internal Layer of Large Pyramidal Cells.*—Cells of this type are rather few, their place being occupied by oval nuclei with little protoplasm.

7. *Layer of Fusiform Cells.*—Few fusiform and occasionally a triangular cell.

DISTRIBUTION.

Lateral Aspect.—The common temporal type of cortex covers all of the lateral face of the temporal lobe, except that portion of the first temporal convolution already described under the audito-sensory and audito-psychic areas. Posteriorly it is bounded by the occipito-temporal sulcus. Above it spreads upward and forward onto the parietal lobe. It comes into relation superiorly with the parietal type of cortex, and here is a triangular area, apex downward, with a base-line of about 60 mm. in length, and a perpendicular of about 30 mm., in which the two types are so confused as to render classification impossible. (Area indicated by both vertical and horizontal lines in Plate III.) The base-line of this triangle is formed by the horizontal branch of the interparietal sulcus and a projected line directly back from there. Below and in front of this unclassified zone the common temporal cortex reaches as far forward as the sulcus interparietalis proprius, which it follows downward for some distance and finally crosses, forming a narrow band along the anterior face of its lower end. Here again is an area of cortex bearing likeness to both temporal and parietal types and passing forward as a triangular patch to include the Rolandic opercle.

Mesial Aspect.—On the mesial aspect the common temporal type of cortex begins posteriorly at the line given for the anterior border of the visuopsychic cortex. Above, in the posterior part, it is separable from the limbic type along a line projected directly anteriorly from the end of the common calcarine trunk. Over it anteriorly lies the specialized cortex of the pyriform lobule, whose outline will be given in more detail later.

Intermediate Postcentral Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Very few fine fibrils.

2. *Supraradiary Plexus.*—Poor fiber content. All fibers of small caliber.

3. *Line of Baillarger.*—Recognized with difficulty.

4. *Radiations of Meynert.*—Short and rather poor. Only an occasional medium-sized fibril.

5. *Interradiary Plexus.*—Fair number of fine fibrils.

6. *Association Fibers.*—Few but strong.

CELL LAMINATION.

1. *Plexiform Layer.*—Not remarkable.

2 and 3. *Layers of Small and Medium-Sized Pyramidal Cells.*—Layers not separable. Cells closely packed, but small and poorly differentiated.

4. *External Layer of Large Pyramidal Cells.*—The large cells in this lamina are definitely smaller than in the postcentral zone. Many undifferentiated cells and small pyramidals.

5. *Layer of Stellate Cells.*—Well represented.

6. *Internal Layer of Large Pyramidal Cells.*—Very few giant cells, even in central parts of the field, and as the posterior border is approached they are entirely wanting. The large cells of this lamina are also fewer than in the postcentral cortex.

7. *Layer of Fusiform Cells.*—Noticeably thinner zone than in postcentral field. Cells few.

DISTRIBUTION.

Mesial Surface.—Intermediate postcentral cortex is found occupying all of the paracentral lobule, behind the postcentral distribution and below it, fusing with the intermediate precentral type just below the end of the sulcus paracentralis. Along the superior margin of the hemisphere it crosses the upturned end of the middle portion of the sulcus cinguli for a short distance.

Lateral Surface.—Bounded anteriorly by the line given for the posterior margin of the postcentral cortex. This line, however, is by no means a definite one, and may have been misinterpreted in places. At the point where the postcentral cortex crosses the mesial border it extends back of the superior division of the postcentral sulcus (which is continuous with the sulcus cinguli) for about 10 mm., but soon moves forward so that this sulcus forms its posterior boundary. This patch is not shown on the plot of the lateral face on account of the angle from which this view is taken. From the bottom of the superior division of the sulcus postcentralis this type of cortex passes in a fairly direct line to the sulcus interparietalis proprius, which it follows for a short distance and then crosses, to be limited by a short sulcus arising and ending in the interparietal, cutting off a small island of cortex. Then it again turns forward, crossing the interparietal and passing just above the end of the inferior division of the postcentral sulcus, and narrowing rapidly to reach the Rolandic fissure at about the level of the lowest point reached by the motor cortex.

Parietal Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Very few delicate fibrils.

2. *Supraradiary Plexus.*—Very poor in fibers, especially in upper layers.

3. *Line of Baillarger.*—Made out with difficulty as a wide band, in places, thin enough in the center to suggest reduplication.

4. *Radiations of Meynert.*—Bundles small, but fairly long and compact. Occasional medium-sized fiber and the remainder fine. No course fibers observed.

5. *Interradiary Zone.*—Fairly rich in fine fibers, but not easily outlined from lower parts of the line of Baillarger.

6. *Association Fibers.*—Moderate number of medium-sized fibers. Large ones rare.

CELL LAMINATION.

1. *Plexiform Layer.*—Not remarkable.

2. *Layer of Small Pyramidal Cells.*—Many cells but rarely one which shows a pyramidal outline.

3. *Layer of Medium-Sized Pyramidal Cells.*—Fairly wide zone. Columnar arrangement to accommodate the radial prolongations.

4. *External Layer of Large Pyramidal Cells.*—Large pyramidal cells fairly numerous. Giant cells absent.

5. *Layer of Stellate Cells.*—Wider zone than in the intermediate postcentral cells. The large cells of this layer are fairly frequent and well formed, and of medium size.

7. *Layer of Fusiform and Triangular Cells.*—Many fusiform and triangular cells mixed with undifferentiated cells, forming a fairly deep lamina.

DISTRIBUTION.

Mesial Surface.—The lower boundary of this type of cortex is found by the parieto-occipital sulcus. The anterior edge comes in relation with the limbic cortex and is difficult to define, on account of the lack of sulcal landmarks. Roughly, however, the limbic type of cortex forms a wide band paralleling the posterior border of the interventricular opening, and near its mid-portion there is a quadrilateral promontory of limbic type jutting out into the precuneus. Above this the parietal projects between the limbic lobe and the paracentral lobule as a narrow triangle, and is sharply limited by the upturned end of the sulcus cinguli, except near the mesial border where the intermediate postcentral overlaps as has been described.

Lateral Surface.—The posterior boundary of the intermediate postcentral serves to outline the parietal field anteriorly. Below it grades off into the common temporal field in the manner already described. Behind it is separated by a wide band of common temporal cortex from the visuopsychic area, until it reaches the mesial border, where it is in apposition to the latter along the parieto-occipital fissure.

Limbic Lobe.

PYRIFORM LOBULE.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Dense mat of fine fibrils with an occasional medium-sized varicose fiber. A few fibers of Martinotti seen.

2. *Supraradiary Zone.*—Very sparsely supplied with fine fibrils and occasionally a larger fiber projected from the radiations.

3. *Line of Baillarger.*—Represented by a very narrow zone in which there is a slight increase in the number of horizontally placed fine fibers, still further increasing and grading into the interradiary plexus below.

4. *Radiations of Meynert.*—Thin and widely separated. Consist of fine fibrils only.

5. *Interradiary Plexus.*—Of about the same fiber caliber as the radiations. Poor meshwork.

6. *Association Fibers.*—Very few.

CELL LAMINATION.

1. *Plexiform Layer.*—This part of the cortex is overlaid by a greatly thickened pia mater containing numerous hyaline globules in clusters. The cell nests in the lower layers of this lamina are rather small, containing as a rule about a dozen cells of the large type. In places the nests occur close together, and the individual groups are more or less elongated, suggesting the formation of a definite lamina instead of isolated clusters.

2, 3 and 4. *Layers of Small, Medium-Sized and (Internal) Large Pyramidal Cells.*—These three layers can not be separated. They form a deep layer of cells of about the same size, which occur more widely apart than in any other region of the cerebrum. The entire cell content seems to have reached a higher developmental differentiation here also, and the oval nuclei with small amounts of protoplasm are very infrequent. Most of the larger cells of this layer, as well as in the internal large pyramidal and fusiform laminæ, are surrounded by groups of satellite cells, in some places eight or ten occurring as a complete ring around a large nerve-cell. Sections from this cortex were stained in phosphotungstic acid hematein after mordanting in ammonium bichromate and picric acid, and revealed a fairly thickly matted meshwork of neuroglia fibrils running in all directions, and distributed fairly generally throughout the whole cortex. These fibrils are for the most part delicate and curly, but scattered throughout are also coarser fibers. They are arranged in no definite direction.

5. *Layer of Stellate Cells.*—Thin, pale lamina showing a few glia cells with one, two or more nuclei, but very few nerve cells.

6. *Internal Layer of Large Pyramidal Cells.*—Thick lamina

with well differentiated large cells lying far apart. Many satellite cells.

7. *Layer of Fusiform Cells.*—Cells of large size and widely separated. Layer deep.

DISTRIBUTION (OLFACTORY AREA OR PYRIFORM LOBULE).

In the gross description of the temporal lobe was mentioned a shallow, vascular impression in the approximate position of the fissura rhinica of Zuckerkandl. Sections through this area show that the vessel groove really overlies a sulcus, but that the opposing walls are so closely approximated and the sulcal depth so slight, that the groove only is recognizable in the gross. Plate IV shows this groove, which is the anterior limit of the lobus pyriformis in those normal brains in which it is found, and which marks sharply the transition here from the olfactory to the common temporal type of cortex. The olfactory type passes backward from here in a narrowing band, ending about opposite the origin of the peduncle by a gradual merging into the adjacent cortex characters.

HIPPOCAMPAL AREA.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Rich supply of fine fibrils. The remainder of this cortex shows a very sparse supply of fine fibrils running in all directions. There is no evidence of a line of Baillarger, and there are no definite radiations, although here and there are found two or three very fine fibrils in a group with a radial direction.

CELL LAMINATION.

1. *Plexiform Layer.*—Thick. A moderate number of clusters containing from 15 to 20 small stellate cells.

Beyond the first layer no laminate arrangement can be made out. The cortex presents a close-packed mass of oval nuclei, with here and there a fully differentiated medium-sized pyramidal cell.

DISTRIBUTION.

In the gross description it will be seen that no hippocampal fissure was recognized, and the microscopic examination fails to reveal any hint of such a structure. The cortex of this region shows the poorest supply of fibers and the greatest paucity of developed cells of any part of the cerebrum, but the occurrence of the characteristic cell nests of small stellate cells in the plexiform layer would seem to justify its inclusion in the description. As to its distribution, it may be said that it is a very narrow and poorly demarcated band following the position which the hippocampal fissure might be expected to assume.

GYRUS FORNICATUS.

In studying the structure of the gyrus fornicatus so little difference was found between the anterior and posterior parts, that they will be described here in one group, and the points of difference indicated in the lamina where they occur.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Fairly richly supplied with very delicate fibrils. Fibers of Martinotti occasional.
2. *Supraradiary Zone.*—Very delicate fibrils in fair numbers.
3. *Line of Baillarger.*—Not recognizable.
4. *Radiations of Meynert.*—Entirely of small fibrils, but fairly thick groups.
5. *Interradiary Plexus.*—Fibers poor in number and of small size.
6. *Association Fibers.*—Very rare. Medium size.

CELL LAMINATION.

1. *Plexiform Layer.*—Fairly broad.
2. *Layer of Small Pyramidal Cells.*—Definite though narrow lamina. Cells closely packed, but many of them are undifferentiated.
3. *Layer of Medium-Sized Pyramidal Cells.*—Deep lamina, but not easily distinguished from the next below.
4. *External Layer of Large Pyramidal Cells.*—This layer is of good depth and contains many typical cells with their axes inclined irregularly. There is a tendency toward pyknosis, but this is not especially marked.
5. *Layer of Stellate Cells.*—Not represented.
6. *Internal Layer of Large Pyramidal Cells.*—This group is not shown as a definite lamina, but near the lower levels of the

external layer of large pyramidals the differentiated cells are noticeably of more frequent occurrence, and at the edges of the field, where the stellate layer again makes its appearance, thereby serving as a good guide to the distribution, it seems to cut off the cells of this lower level from the overlying ones, the former continuing as the internal large pyramidal layer of the adjacent cortex. In other words, the deep lamina of large pyramidal cells seems here to represent both the internal and external layers of other parts with the dividing line of small stellate cells omitted. This view is in opposition to Campbell, who holds that the internal large pyramidal layer is lacking in this cortex as well as the stellate.

7. *Layer of Fusiform Cells.*—It is in this layer that the difference between the anterior and posterior parts of the gyrus is evident. Anteriorly the layer is a thick one with many well differentiated fusiform and triangular cells, and with some pyknotic or chromophilous spindle cells. From Campbell's illustration and description, it seems probable that these elements are greatly reduced in number. Very few low-power fields were found which showed more than one cell of this kind.

Posteriorly the layer is considerably thinner and lacks the chromophilous cells.

DISTRIBUTION.

The limbic type of cortex occupies all of the gyrus fornicatus. In addition it spreads anteriorly over the next adjacent gyrus. Above it follows out along the diverging part of the anterior division of the sulcus cinguli as far as the communicating branch between this division and the second. The second division forms its boundary back to the paracentral lobule, where a wedge of parietal cortex is interposed and from there backward and downward it passes as a band of fairly even width, except for the quadrilateral patch mentioned in the description of the parietal boundary.

Intermediate Precentral.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Fairly numerous small fibrils and occasionally a coarse varicose fiber.

2. *Supraradiary Zone.*—Small fibers rather sparsely scattered.

3. *Line of Baillarger.*—Poor but definable. Chiefly long evenly medullated fibers.

4. *Radiations of Meynert.*—Strong bundles of fine varicose fibers containing one or two evenly medullated fibers of medium size.

5. *Interradiary Plexus.*—Well marked. Fibers of small caliber.

6. *Association Fibers.*—Numerous coarse fibers running in all directions.

CELL LAMINATION.

1. *Plexiform Layer.*—Not remarkable.

2 and 3. *Layers of Small and Medium-Sized Pyramidal Cells.*—Wide zone, but not recognizable as two laminæ. Majority of cells well differentiated.

4. *External Layer of Large Pyramidal Cells.*—Wide lamina containing many large well differentiated cells. Considerable pyknosis.

5. *Layer of Stellate Cells.*—Poorly defined.

6. *Internal Layer of Large Pyramidal Cells.*—This layer is a thin one, but its cells are large and well formed. Their size is greater than that of the cells in the external layer, but definitely smaller than the homologous cells in the precentral cortex, and there are no giant cells present.

7. *Layer of Fusiform Cells.*—Very poorly represented. Cells few and small.

DISTRIBUTION.

Mesial Surface.—The sulcus paracentralis forms a posterior boundary of this type of cortex, and its extent is also limited by the end of the dorsal portion of this sulcus where it comes in relation below the motor and postcentral types with intermediate postcentral cortex. Below, it follows the middle division of the sulcus cinguli forward to the communicating sulcus, between this division and the anterior, where it turns upward and is sharply limited from the limbic cortex. The portion of the first frontal gyrus immediately overlying this point shows characters which are common both to this type and to the frontal, and no definite outline is possible.

Lateral Surface.—On this aspect the anterior boundary of the motor cortex limits the intermediate precentral posteriorly. Its anterior line above is hard to make out, and a considerable area remains unclassified. This is shown on the plot as the triangular patch on the first frontal gyrus containing both small and large dots. Below this zone on the second frontal this type forms a skirt about 25 to 30 mm. wide in front of the precentral cortex. Still lower the band narrows, and is limited anteriorly by the inferior division of the precentral sulcus. Below the motor field on the posterior border, the intermediate cortex touches the fissure of Rolando, and comes into relation with mixed parietal and common temporal cortex covering the Rolandic opercle. The intermediate crosses the precentral sulcus on a level with the lowest point reached by the motor cortex and passes forward to include the three opercular gyri surrounding the anterior limb of the fissure of Sylvius. Below, this patch ends at the fronto-marginal sulcus of Wernicke.

Frontal Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Few small fibrils.

2. *Supraradiary Zone.*—Scattered small fibers chiefly horizontal in direction.

3. *Line of Baillarger.*—Barely definable. Fibers small.

4. *Radiations of Meynert.*—Fairly strong clusters of fine fibrils with only an occasional medium-sized fiber.

5. *Interradiary Plexus.*—Poor network of fine fibrils.

6. *Association Fibers.*—Few long evenly medullated fibers of medium size.

CELL LAMINATION.

1. *Plexiform Layer.*—Not remarkable.

2 and 3. *Layers of Small and Medium-Sized Pyramidal Cells.*—Fairly thick layer, but with very few developed cells.

4. *External Layer of Large Pyramidal Cells.*—The cells of this layer are numerous, and among them are a fair proportion of large pyramids of good form.

5. *Layer of Stellate Cells.*—Noticeably wider than in the intermediate precentral field.

6. *Internal Layer of Large Pyramidal Cells.*—The cells of this layer show the best differentiation of any lamina of this field. They are of fair size with strong basal processes, and occasionally a few chromophilic particles.

7. *Layer of Fusiform Cells.*—Zone narrow. Poor in cells.

DISTRIBUTION.

Mesial Surface.—Beginning behind in the unclassified zone mentioned in the distribution of the intermediate precentral zone it passes forward, separated from the limbic type by the anterior division of the sulcus cinguli, for about 70 mm., where it fuses imperceptibly with the prefrontal.

Lateral Surface.—On this aspect the frontal type forms a band about 30 cm. wide, skirting the intermediate precentral. Where the latter field passes forward over the anterior Sylvian opercular gyri below, the frontal area is very considerably narrowed and remains so as it passes over to the orbital surface, including there only the narrow gyrus lying to the mesial side of the fronto-marginal sulcus and that part of the adjacent gyrus not occupied by intermediate precentral cortex.

Prefrontal Cortex.

FIBER ARRANGEMENT.

1. *Zonal Layer.*—Very poor supply of poor fibers.

2. *Supraradiary Zone.*—Rare fine fibril.

3. *Line of Baillarger.*—Not recognizable.

4. *Radiations of Meynert.*—Clusters of three or four short, fine fibers.

5. *Interradiary Plexus.*—Few scattered, very fine fibers.

6. *Association Fibers.*—None.

CELL LAMINATION.

1. *Plexiform Layer.*—Narrow.

2, 3 and 4. *Layers of Small, Medium-Sized and (External) Large Pyramidal Cells.*—These layers form a fairly deep zone which is not separable into different laminæ. The cells are numerous and close-packed, but for the most part with oval nuclei only, with little or no protoplasm. Frequently the nuclei are more or less vesicular in type. In the lower layers an occasional large pyramidal cell can be made out, and where they are seen they are well formed and of fair size.

5. *Layer of Stellate Cells.*—Wider than frontal.

6. *Internal Layer of Large Pyramidal Cells.*—This layer compares very closely with the description of the second, third and fourth layers given above except that it is considerably narrower and that fully differentiated large pyramidal cells are slightly more numerous.

7. *Layer of Fusiform Cells.*—Narrow belt containing few small cells.

DISTRIBUTION.

The distribution of the prefrontal is perhaps best outlined by the statement that it occupies all of the frontal pole anterior to the limits described for the limbic and frontal cortex on the mesial surface, and by the frontal on the lateral aspect. On the orbital surface it covers all of the gyri except the narrow band of frontal type along the fronto-marginal sulcus posteriorly.

The homology between the fissures and sulci of the brain under consideration and the normal, will be easily seen from the foregoing description, but a few points of sulcal arrangement deserve especial note.

The anastomosis between the Sylvian fissure and the first temporal sulcus is mentioned by Van Hersecke. He quotes from Giacomini four cases out of 400 brains, while Chiarugi is credited with the statement that it was found in four cases out of 32 brachycephalics and one out of ten dolichocephalics.

The upward prolongation of the first temporal sulcus is of more common occurrence. Eberstaller says that not infrequently the ascending part of this sulcus joins the pars horizontalis of the interparietal, thus cutting in two the gyrus angularis. Ecker says that the first temporal extends backward and upward to very different distances in different cases. Its posterior extremity lies as a rule higher than the Sylvian, and in every case the gyrus angularis winds around it to be continued into the second temporal. Wilder shows an illustration of a brain with a greatly extended supertemporal sulcus, and in Van Hersecke's article is a reproduction of an illustration of the brain of the Venus Hottentoti of Gratiolet, which bears a similar peculiarity.

The interparietal follows the common type as described by Cunningham, *i. e.,* all three parts confluent. This arrangement Cunningham quotes as present in 56 per cent of 62 brains examined.

Many authors consider the normal origin of the interoccipital of Dejerine to be in the interparietal. Cunningham calls it the ramus occipitalis of this fissure. Wilder, however, gives it as arising from a stipe and ramus independent of the interparietal, and this is the arrangement followed here.

The sulcus mentioned in the gross description as arising in the temporo-occipital angle and continuing back to fuse with the inferior branch of the first temporal, is probably the occipito-temporal of Lussana. Wilder shows a brain with a somewhat similar sulcus and says that it may possibly be considered as the homologue of the exoccipital or fissure of Wernicke. An even stronger statement seems justifiable in the present case when the distribution of the visuopsychic type of cortex is considered along with the position of the fissure. Fig. 1 gives a rather misleading idea of the relation of this fissure to the first temporal, due to the distortion of the projection. Plate III is more apt, and beyond the point of junction of these two sulci, the direction is almost as much like a continuation of the occipito-temporal as of the first temporal. Although the true sulcal character of this cleft is lost before it reaches the mesial border, it is continued as a vascular groove up to the angle where its contained vessel enters the notch formed by the end of the occipito-parietal sulcus on the mesial surface. The delimitation on the lateral surface of the visuopsychic type of cortex along this fissure adds interest to its possible homology to the exoccipital sulcus of the ape's brain, which there serves as the anterior boundary of the same type of cortex. This homology and its possible significance have given rise to considerable controversy. Mendel, in his article entitled "Ueber die Affenspalte," concludes that a homologous fissure occurs in man, both sound-minded and otherwise, but no pathological significance has been demonstrated.

The vascular groove occupying the position of the fissura rhinica of Zuckerkandl is, as has been pointed out, undoubtedly that of a vessel which lay in that sulcus before the internal pressure of the enlarging ventricle had manifested itself to such an extent as to obliterate the gross evidence of the existence of the sulcus. Microscopically the sulcal construction is readily observable.

No trace, either gross or microscopical, could be found of the hippocampal fissure.

The downward displacement of the calcarine fissure is mentioned under the discussion of the distribution of the visuosensory type of cortex, and is explainable by the greater distension of those portions of the occipital lobe above it.

The existence of the vertical sulcus at the end of the calcarine is worthy of mention. This is the sulcus retrocalcarinus verticalis of Elliot Smith, called the fissura extrema by Seitz, and the retrocalcarine by Monakow.

In the normal cerebrum the transition from one type of cortical lamination and fiber arrangement to the next, is so gradual that with a few exceptions it is difficult to outline even approximately the limits of the fields. Bevan Lewis says " no abrupt passage from one form of cortical lamination to that of another is ever seen in the convolutions of the vault. Changes in type are gradually assumed, and no distinct boundary line exists to indicate an exact line of demarcation. The structure peculiar to one region gradually fades and blends with the arrangements which foreshadow the architecture of adjacent realms, and thus we obtain transition regions."

In the present case the pathological alteration of the cortical structures is such that in some places it serves as an aid, while in others a hindrance to limitation. In certain areas the internal pressure by flattening and narrowing the cortex has served to compress and render more compact some structures, thus accentuating their prominence. The comparative density of the line of Gennari is a striking example of this. Fig. 6 is a low-power microphotograph showing a portion of the calcarine field with the prominent line of Gennari and radiations of Meynert.

In many areas, however, the number of nerve-cells represented only by embryonal or imperfectly developed forms makes their classification more difficult. Here again, however, enters a factor which is absent in normal cortex: the proportion of fully developed cells seems to vary with the importance of the field. Thus the large common temporal and parietal areas are very poorly supplied with differentiated cells, though the total cell content is remarkably rich. Their fiber content, as elsewhere, varies directly with the number of differentiated cells. This contrast of cell development between areas serves in some places as a marked aid; thus, in limiting the visuopsychic from the common temporal fields along the occipito-temporal sulcus, it is a factor of importance. In other places, however, the same condition interferes; for instance, between the common temporal and the parietal fields and along the outskirts of the intermediate pre- and postcentral zones. In regard to the distribution of the cortical fields, nothing need be added to the description already given under each separate area.

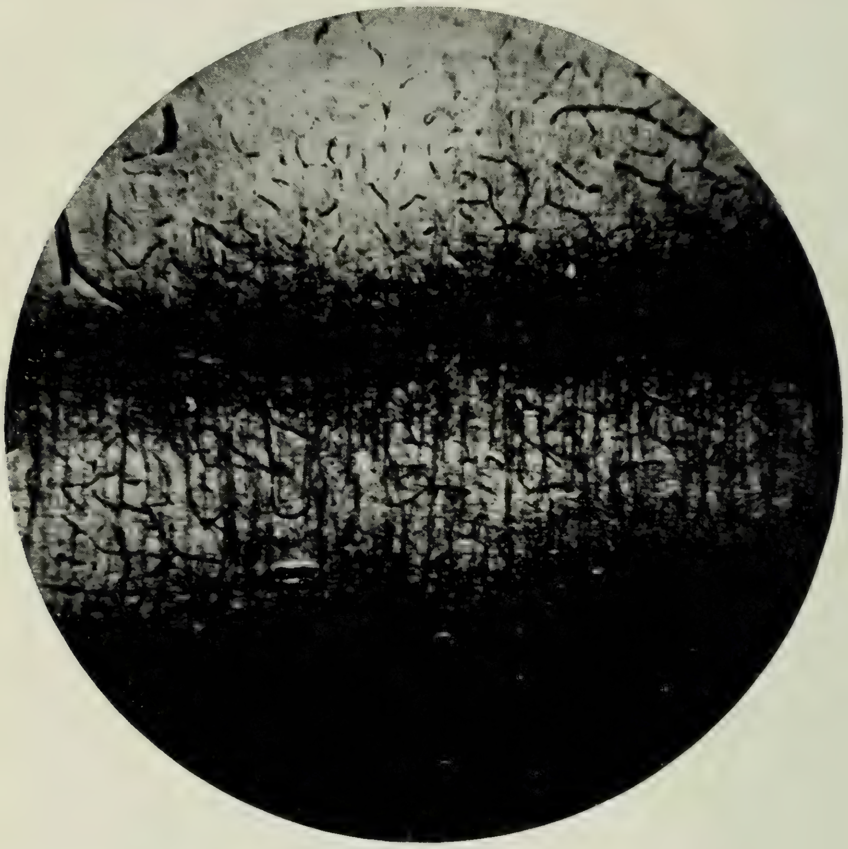


FIG. 6.—Low-power microphotograph of a field in the visuosensory area.

Reference has been had to Flechsig's charts of the time of myelinization of the cerebrum, and an attempt has been made to correlate the cortical development of the various localities with his findings, and in general the comparison is apt, though there are some points of difference.

It will be readily seen from the illustrations that with the exception of those parts of the occipital and temporal lobes where the attenuation is most marked, the complement of fissures and sulci is equal to that of the normal at least, and even in the two excepted areas, the microscope gives evidence of the original existence of sulci which have disappeared during the alterations wrought by the pressure. The full development of the sulci is not reached in the normal brain, according to Cunningham, until one month after birth, so that it seems reasonable to deduce that the internal pressure had not progressed very far before that time. On the other hand the enlargement of the head indicates that the pressure was active before the ossification of the cranial sutures, thus placing the time of appearance of the pressure effects between those two periods.

As to the time of the appearance of the lesion in the aqueduct, there is no further evidence. Its type is such that no definite diagnosis can be given. The microscopic picture is one which is consistent with the diagnosis of a chronic inflammatory process, but there is no evidence to exclude the superimposition of a chronic inflammation, arising from pressure, on a previously existing developmental fault. The presence, through the obstruction, of patent neuroglia-lined canals may explain why the patient lived to maturity, and in this event a gradual narrowing of these channels by added inflammatory deposit or by contraction of the glial cicatrix already present, would readily explain the slow retrograde course of the disease, *i. e.,* the increasing imbecility, etc. Bourneville et Noir report a case of a child who, until the age of seven months was apparently normal, then developed convulsions and *pari passu* an enlargement of the head. The child lived nine years with occasional epileptic seizures. At autopsy the aqueduct of Sylvius was found to be occluded. The fissures and gyri have their normal distribution and the lower structures are normal. This would seem like a clear case of postnatal development, while on the other hand E. Cantley describes a child that lived four months after birth with its prosencephalon represented by a membranous bag of fluid. The crura, pons and lower structures were present. Such a condition is explainable only on the ground that the obstruction was present before the cerebral structures were advanced in their development.

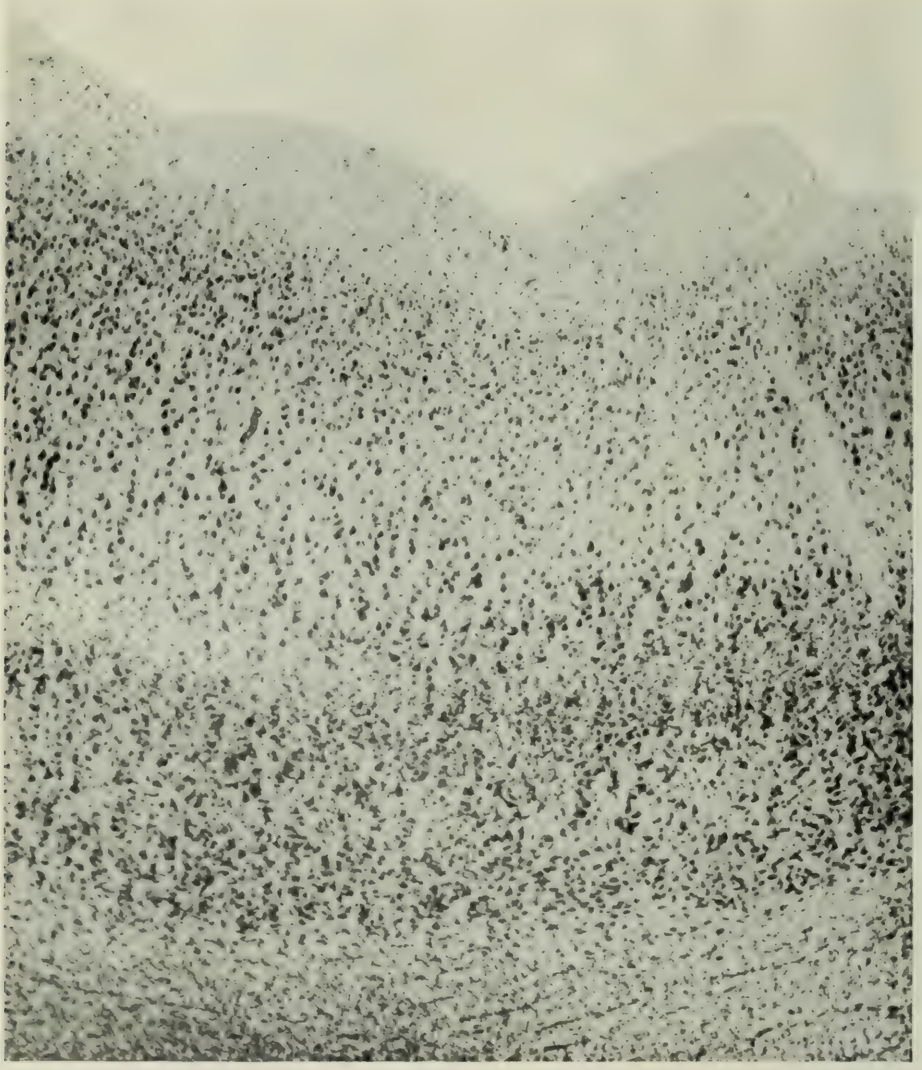


FIG. 7.—High-power microphotograph. Limbic lobe. Showing cell richness of areas where attenuation of cortex is marked.

In several reported cases of hydrocephalus, mention is made of various degenerations in the spinal cord and medulla, usually in the pyramidal tracts, occasionally in other paths, giving the picture of a secondary degeneration. In the present instance no such alterations were observable.

Huseck and Kramer describe a case in a patient of 40 years who was practically a helpless idiot. The legs were contractured and at autopsy there was found a bilateral degeneration of the pyramidal tracts from the peduncle to the sacral region. The sulci are fairly well homologized. The microscopic report gives the cells as close-packed but normal, fibers lessened in number. The ependyma is thickened and contains many corpora amylacea.

G. Anton also adds, in a list of three congenital cases, one associated with atrophy of one olive, one side of the cerebellum, and one cerebellar tract in the cord.

Touche gives the report of an autopsy on a 29-year old hydrocephalic who had been apparently normal to his fourth year, when the disease manifested itself with an acute onset and convulsions. The fissures and gyri are easily made out and not anomalous. The aqueduct of Sylvius is obliterated. There is no microscopic report and, although the patient was paralyzed in the lower extremities, no record of the findings in the cord.

Spiller reported a case in 1902 of a patient who lived to the age of 19. The aqueduct was to the naked eye entirely closed, but microscopically, as in the present case, a small canal was demonstrable through the obstruction. In an article by the same author in association with Allen in 1907, is found a description of a similar condition in a patient of 62 years who was supposed to have been born hydrocephalic. To quote from this report: " The aqueduct was almost occluded, this occlusion being probably a congenital malformation because the cavity was well lined throughout by a layer of ependymal cells, which would hardly be the case if the occlusion were caused by proliferation of neuroglia." The occurrence of canals lined by ependyma in gliomata, and the cutting off of ependymal pockets in marked cases of granular ependymitis, are recognized, so that this evidence quoted in support of a malformation carries less weight than the time of onset and the degree of development of the affected structures.

There are reports galore in the literature of cases of hydrocephalus, but the great majority are merely statements of the case histories with or without the gross autopsy findings, and with no microscopic examination.

The question of etiology in early hydrocephalus is one which can best be approached through statistical methods. The true hereditary origin has been suggested, but receives slight substantiation. Hereditary syphilis and congenital malformations are generally conceded as the leading causes. Spiller, in discussing one of his cases, suggests the toxin of the tubercle bacillus as a possible cause. Injuries during labor, acute toxemias in the mother, and uremia gravidarum are also mentioned as causative, while chronic leptomeningitis, either tubercular or otherwise, is frequently the cause of those cases where the obstruction is at the foramina of Magendie and of Key, and Retzius, in which case the fourth ventricle is included in the dilatation. Endocranial tumors may also produce on obstruction.

Conclusions.—The case is one of advanced hydrocephalus, but the surface anatomy and the cortical histology can be readily homologized with the normal. The variations of sulcal arrangement are such as are met occasionally in the normal brain. Alterations of the distribution of cortical fields with few exceptions are inconsiderable. The lesion was a partial obliteration of the aqueduct of Sylvius and might have been inflammatory in character or a malformation plus inflammation. The time of manifestation of pressure results is evidently between the end of the first month of postnatal life and the time of ossification of the cranial sutures, but the time of occurrence of the lesion can not be set so definitely.

REFERENCES.

A. CEREBRAL ANATOMY.

1. Barker, L. F.: The nervous system, 1899.
2. Quain: Anatomy, Vol. II, Part I, Brain and cord, E. A. Schäfer, 1902.
3. Cunningham, D. J.: The interparietal sulcus, Journ. Anat. and Phys., 1890; On cerebral anatomy, Brit. Med. Journ., Aug., 1890.
4. Gowers, W. R.: Diseases of the nervous system, Vol. II.
5. Dejerine, J.: Anatomie des centres nerveux, 1894.
6. Obersteiner: Nervöse Centralorgane, 1901.
7. Dalton: Topographical anatomy of the brain, 1885.
8. Smith, Elliot: Morphology of the retrocalcarine region of the cortex cerebri, Proc. Roy. Soc., Vol. LXXIII, 1904.
9. Eberstaller, O.: Zur Oberflächenanatomie der Grosshirn-Hemisphären, Wien. Med. Blätter, 1884.

10. Van Hersecke, G: La morphologie des circonvolutions cérébrales, Lille, 1891.
11. Jensen, J.: Die Furchen und Windungen der menschlichen Grosshirn-Hemisphären, Zeitsch. f. Psych., 1871.
12. Valenti, Giulio: Contributo allo studio delle scissure cerebrali, Soc. Toscana di Sc. Nat., Vol. XI, 1891.
13. Ecker: Die Hirnwindungen des Menschen, 1883.
14. Wilder, B. G.: Human cerebral fissures, their relations and names and methods of studying them, Am. Naturalist, Oct., 1886; The paroccipital, a newly recognized fissural integer, Journ. Ment. and Nerv. Dis., Vol. XIII, 1886.
15. Mendel: Ueber die Affenspalte, Neurolog. Centralbl., 1883.
16. Turner, W.: The convolutions of the human cerebrum, Edinburgh, 1866; The convolutions of the brain, Journ. Anat. and Phys., Vol. XXV, 1890.
17. Rüdinger, N.: Ein Beitrag zur Anatomie der Affenspalte, Henle's Festschrift, p. 191, 1882.

B. Cerebral Embryology.

1. Beer: On the development of the Sylvian fissure in the human embryo, Journ. Anat. and Phys., 1890.
2. His, W.: Die Formentwicklung des menschlichen Vorderhirn, Abhandl. d. Königl. Sachs. Gesch., Bd. XV, 1889.
3. Flechsig, Paul: Neue Untersuchung über die Markbildung in den menschlichen Grosshirnlappen, Neurolog. Centralbl., No. 21, 1898; Weitere Mittheilungen über die entwickelungsgeschichtlichen (myelogenetischen) Felder in der menschlichen Grosshirnrinde, Neurolog. Centralbl., March 1, 1903.

C. Comparative Anatomy.

1. Cunningham, D. J.: The surface anatomy of the primate cerebrum, Memoirs Roy. Irish Acad., No. 8, 1889.
2. Broca, Paul: Anatomie comparée des circonvolutions cérébrales, Revue d'Anthropologie, 1878; Memoirs sur le cerveau de l'homme et des primates, Paris, 1888.
3. Giacomini: Sur le cerveau d'un chimpanzé, Arch. Ital. de Biologie, Vol. III, 1890.
4. Lussana: Circonvolutionum cerebralium anatomes humana et comparata, Patavia, 2d edition, 1888.
5. Rohon, J. V.: Zur Anatomie der Hirnwindungen bei den Primaten, 1884.

D. Cortical Histology.

1. Campbell: The localization of cerebral function, Cambridge, 1905.
2. Hammarberg, Carl: Studien über Klinik und Pathologie der Idiotie, Upsala, 1895.
3. Cajal, S. Ramón y: Hirnrinde des Menschen, German translation by Dr. J. Bresler, Leipzig, 1900.

4. Lewis, Bevan: On the comparative structure of the cortex cerebri, Brain, Vol. I, 1879.

5. Kaes, Th.: Beiträge zur Kenntniss des Reichthums der Grosshirnrinde, Arch. f. Psy. u. Nervenkr., Bd. XXV, H. 3, 1893.

6. von Monakow: Gehirnpathologie, Wien, 1897.

E. Localization.

1. Campbell: See D. 1.

2. Sherrington and Grünbaum: Observations on the physiology of the cerebral cortex of some of the higher apes, Proc. Roy. Soc., LXIX, 1901; LXXI, 1903.

3. Mills, C. K.: The physiological areas and centers of the cerebral cortex of man, with new diagrammatic schemes, U. of Pa. Med. Bull., May, 1904; A new scheme of the zones and centers of the human cerebrum, Journ. A. M. A., October 4, 1902.

4. Lewis, Bevan and Clarke, Henry: The cortical localization of the motor area of the brain, Proc. Roy. Soc., No. 185, 1878.

F. Hydrocephalus.

1. Spiller, Wm.: Two cases of partial internal hydrocephalus from closure of the interventricular passages, Am. Journ. Med. Sc., p. 44, July, 1902.

2. Spiller, Wm. G. and Allen, A. R.: Internal hydrocephalus with report of two cases, Journ. A. M. A., Vol. XLVIII, No. 15, 1907.

3. Anton, G.: Zur Anatomie des Hydrocephalus, Wien. Med. Jahrb., 1888.

4. Bourneville et Noir: Hydrocephalie, Le Progrès Médical, July, 1900.

5. Touche: Hydrocephalie interne, Bull. de la Soc. Med. des Hôpitaux de Paris, 1902.

6. Berkley, H. J.: Hydrocephalus in the adult, Amer. Journ. of Insanity, October, 1903.

7. Huseck and Kramer: Ein Hydrocephalus ungewöhnlichen Umfangs, Arch. f. Psy. u. Nervenkr., 1889.

8. Cantley, E.: Congenital hydrocephalus, Brit. Med. Journ., Vol. I, 1900.

9. Bar, M. P.: Forme rare d'hydrocephalie, Gaz. Hebd. de Med. et Chir., No. 57, 1901.

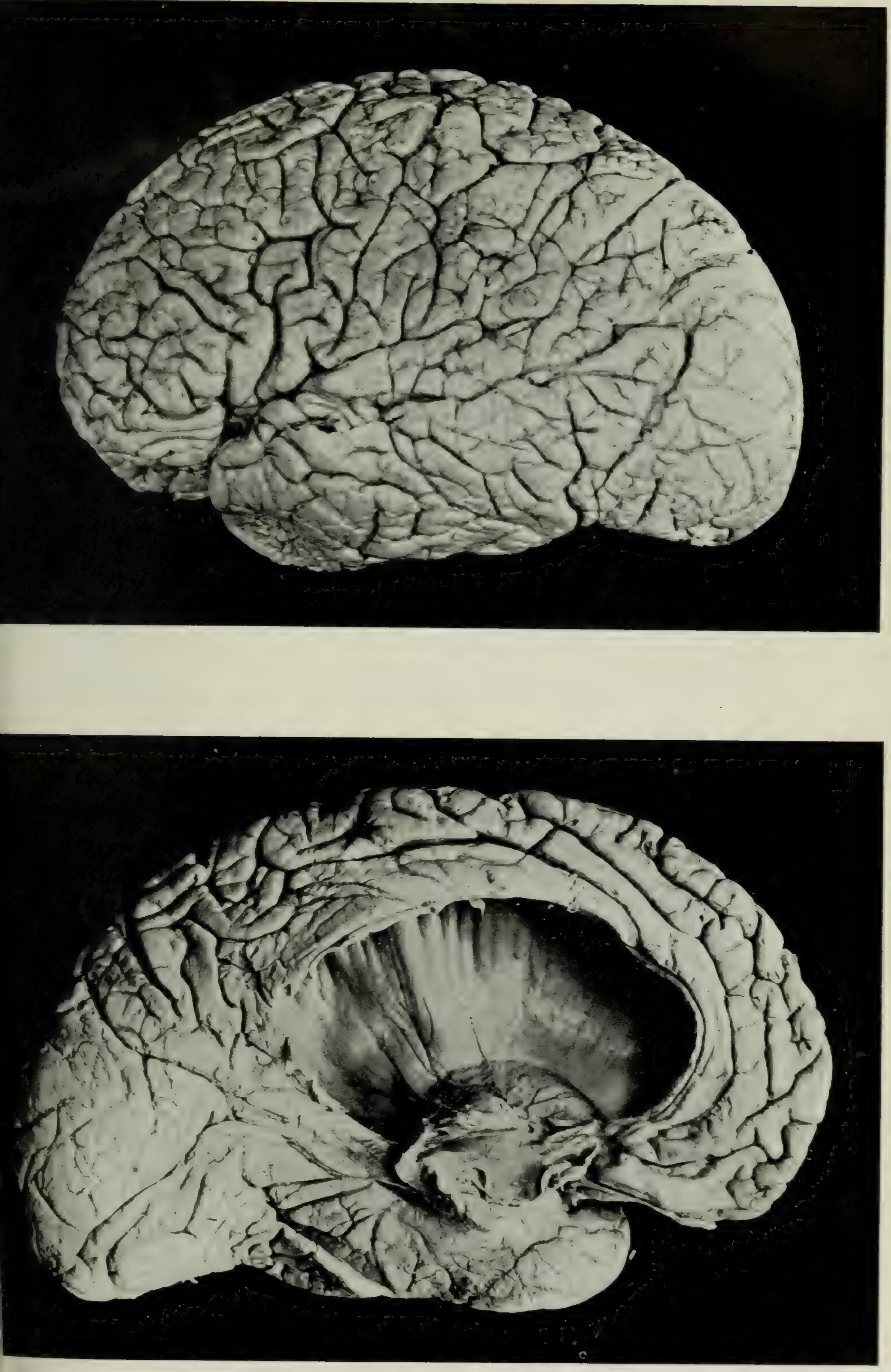
10. Galatti, Demetrio: Klinische Beitrag zum Hydrocephalus syphilitischen Ursprungs, Wien. Klin. Wochensch., No. 25, 1904.

11. D'Astros: Les hydrocephalies, Paris, Steinheil, 1898.

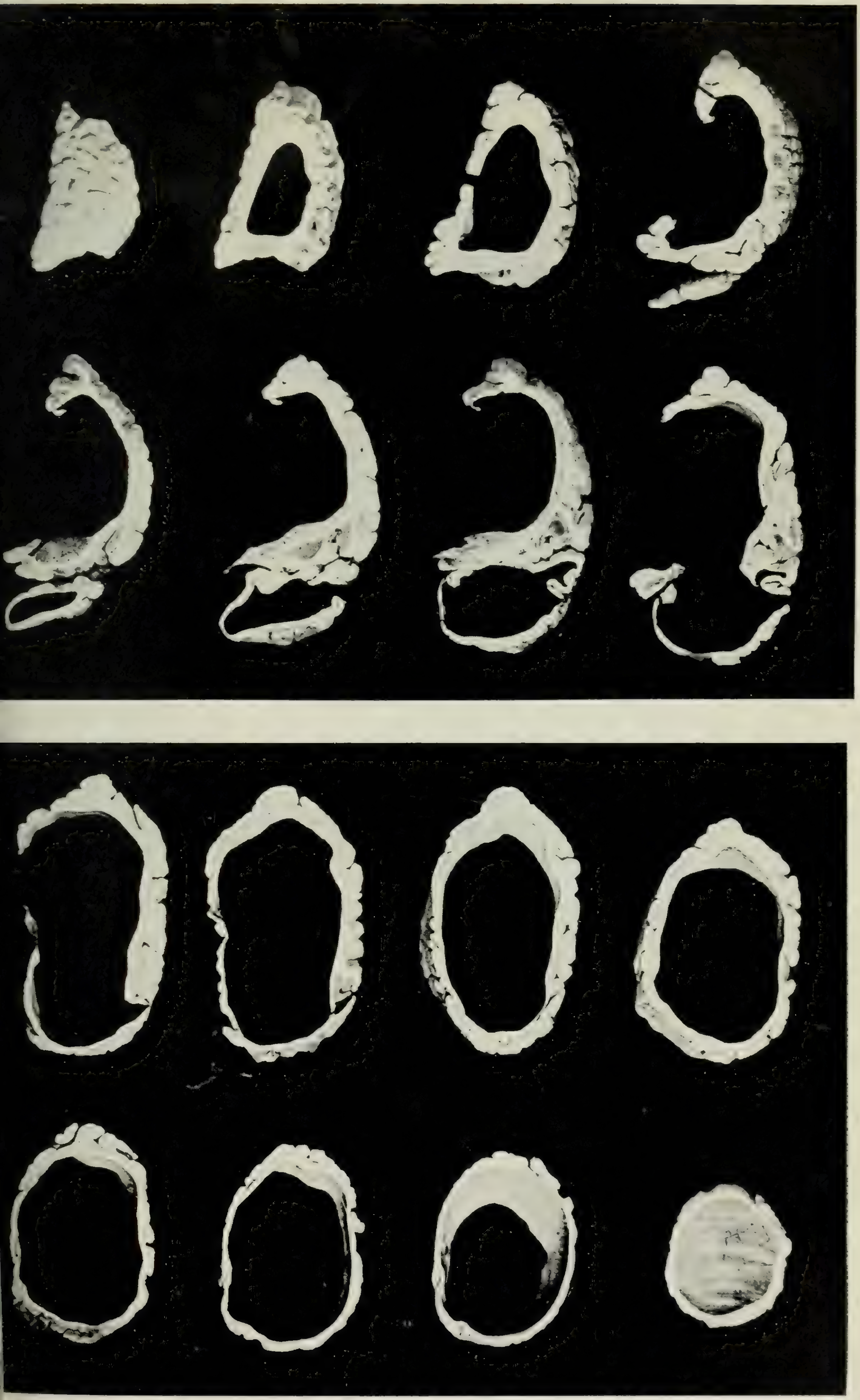
12. Chiari, H.: Veränderung des Kleinhirns, des Pons und der Medulla Oblongata nach congenital Hydrocephalus, Wien. Denksch. der Acad. der Wissensch., 1895.

13. Southard, E. E. and Roberts, W. F.: A case of chronic internal hydrocephalus in a youth, Journ. Nerv. and Ment. Dis., February, 1904.

14. Fuchs, Alfred: Ein fall von sogenannten idiopathischen Hydrocephalus chronic internus, Arb. a. d. Neurolog. Inst. a. d. Wien. Univ., XI.



Photographs of the Lateral and Mesial Aspects of the Left Hemisphere.



Gross Horizontal Sections of the Left Hemisphere.

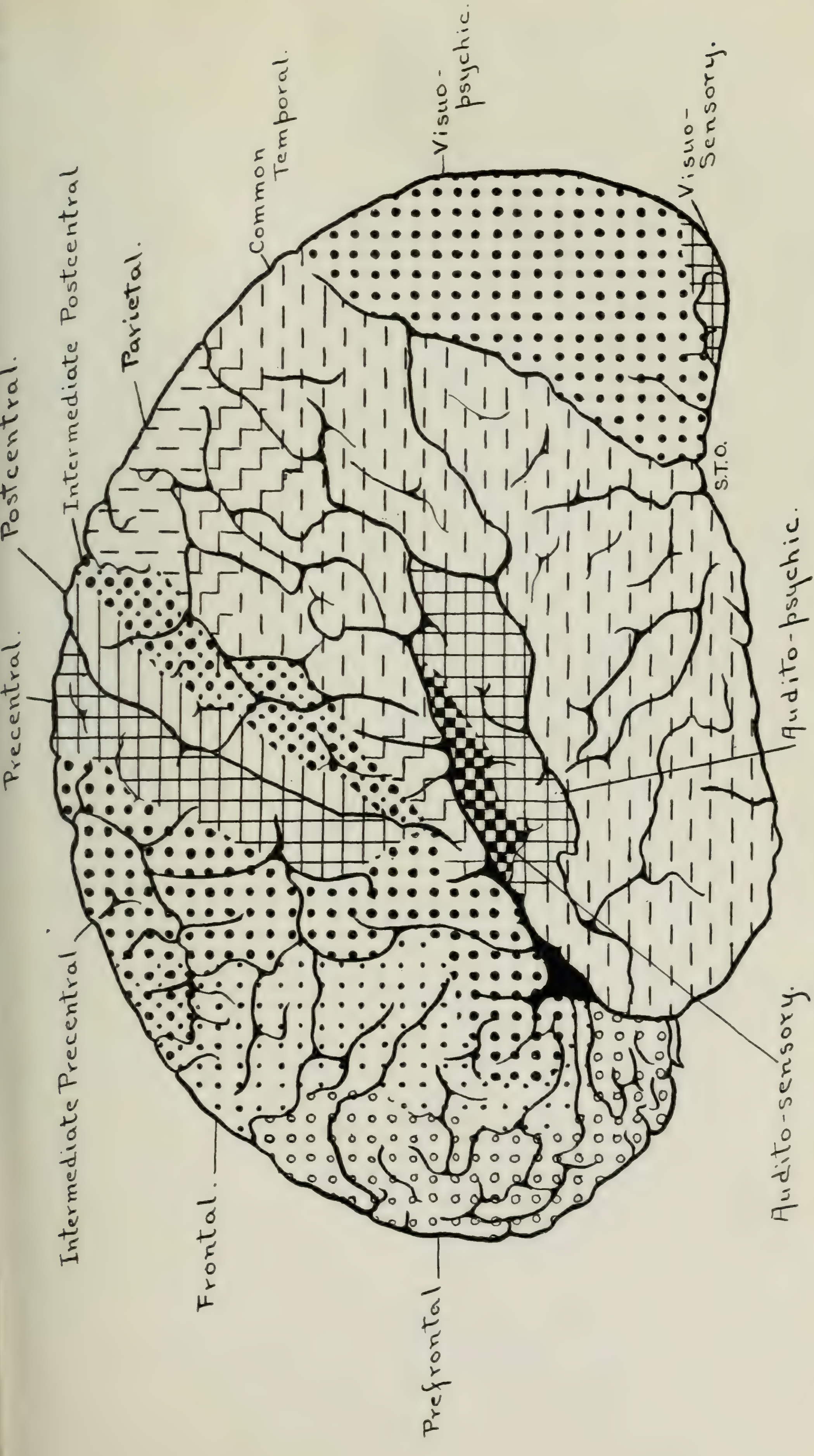


CHART SHOWING DISTRIBUTION OF VARIOUS TYPES OF CORTEX. LATERAL ASPECT.

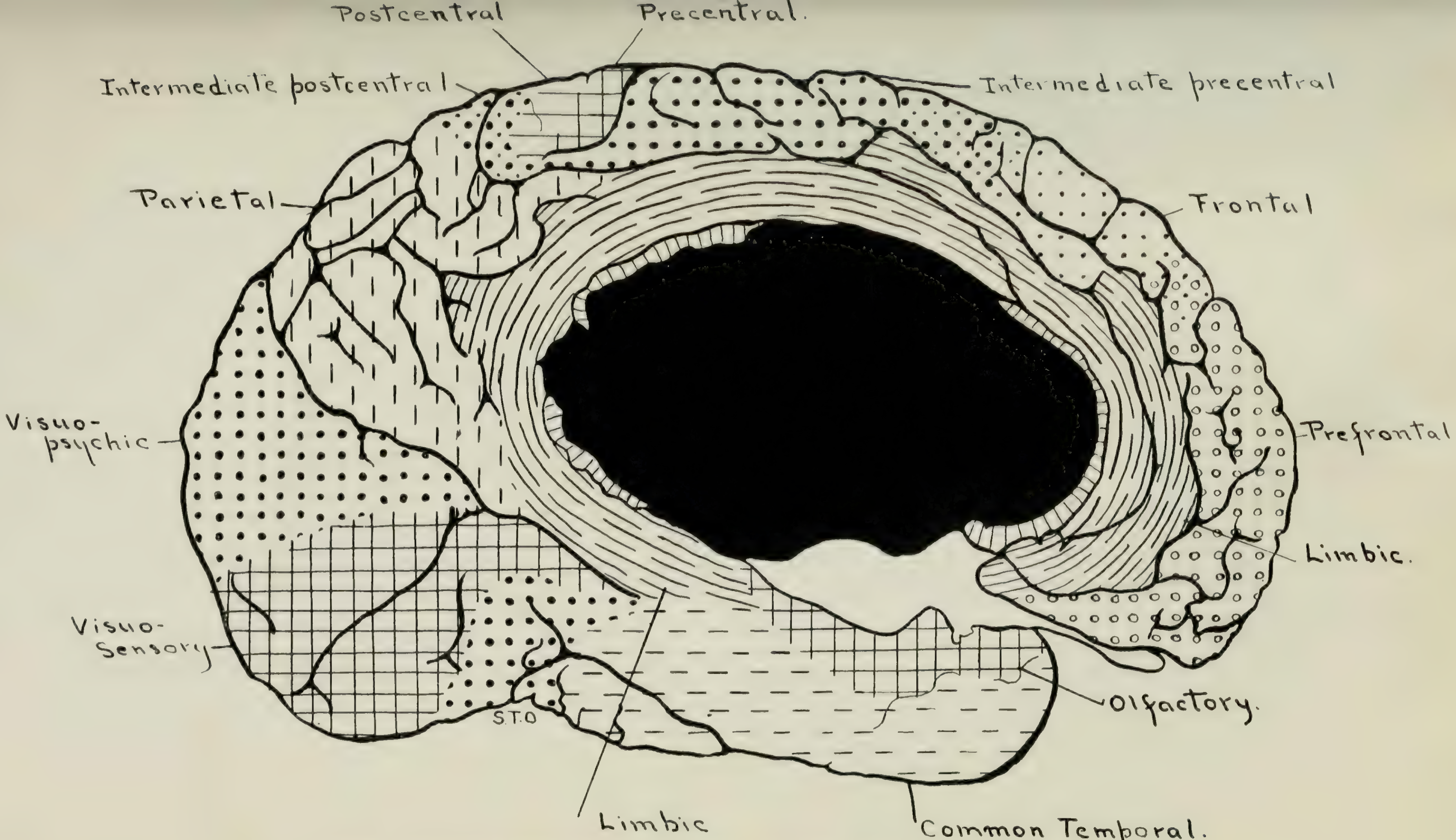


Chart Showing Distribution of Various Types of Cortex. Mesial Aspect.

CLINICAL AND ANATOMICAL ANALYSIS OF 23 CASES OF INSANITY ARISING IN THE SIXTH AND SEVENTH DECADES WITH ESPECIAL RELATION TO THE INCIDENCE OF ARTERIOSCLEROSIS AND SENILE ATROPHY AND TO THE DISTRIBUTION OF CORTICAL PIGMENTS.

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(From the Pathological Laboratory of the Danvers Insane Hospital.)

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CLINICAL AND ANATOMICAL ANALYSIS OF 23 CASES OF INSANITY ARISING IN THE SIXTH AND SEVENTH DECADES WITH ESPECIAL RELATION TO THE INCIDENCE OF ARTERIOSCLEROSIS AND SENILE ATROPHY AND TO THE DISTRIBUTION OF CORTICAL PIGMENTS.*

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I. General Statement.

The diagnosis of mental disease is not anywhere more difficult than in persons attacked in the fifth, sixth and seventh decades in life. This difficulty is paramount in the fifth decade, particularly in women, and is assumed to be connected with altering processes of growth and internal secretory changes. The problems shift their ground in the sixth and seventh decades and are particularly complicated by the suspicion of premature old age changes.

We have chosen to analyze the clinical and anatomical material, accessible to us, from cases developing or assumed to develop insanity in the sixth and seventh decades. We have been looking, consequently, toward the relation of these phenomena to senile phenomena rather than to the more complex or obscure conditions of earlier decades.

We have omitted cases of dementia paralytica, cerebral tumor, and extensive focal brain lesions from consideration in this group. The 23 cases here presented occurred in a series of 472 autopsied cases (1902-1907) at the Danvers Insane Hospital and were chosen on the ground of probable onset of mental disease in the sixth or seventh decade, as shown by reference to case-histories. All the cases had been observed by one (or both) of the writers or (in a few instances) by assistant physicians who were personally consulted concerning the fitness of these cases for the chosen group. The 23 cases represent a sifting out from about 50 autopsied cases which were thought at first to correspond to our criteria but were found actually to represent instances of paralytica dementia or other coarse brain disease. A few cases, clinically appropriate, were omitted on account of deficiency in the anatomical records. The group represents about 5 per cent of the autopsies performed.

II. Case Material.

We present 23 cases of insanity arising in the sixth or seventh decade. The clinical histories are much condensed, and the autopsy protocols are given in summary form. These cases are arranged according to a tentative grouping, adopted for convenience at the outset:

Alcoholic	2	cases.
Paranoic	5	"
Delirious	4	"
Maniacal	3	"
Depressed	9	"
Total	23	cases.

I. *Alcoholic Conditions.*

Case 1 is a man whose insanity developed at 57 and who died at 63, after five years in the hospital.

No history of neuroses, psychoses or intemperance in immediate family.

He was a bright companionable man in early life and since boyhood had been intemperate in the use of alcohol. Because of drinking habits, he failed in his business as undertaker one year before admission. He continued to drink hard and became much demented. He had no memory for recent events and showed well-marked fabrication.

On admission he was well nourished. Physical examination was negative excepting for sluggish pupillary reactions and diminished tendon reflexes. There was no history of lues.

He was neat and orderly in manner, and talked coherently in response to overtures, but there was practically no spontaneous production. He was disoriented for time, place, and persons. His memory was almost a blank, and he fabricated to supply deficiency. He was not hallucinated and never showed any well-defined delusions. He had no grasp on surroundings or any insight, and was always amiable. He never showed any interest in surroundings or engaged in any work or amusement of his own initiative. There was no apparent change in his mental condition before death.

Anatomical Diagnoses.

Chronic valvular endocarditis.
Calcification of bronchial lymph nodes.
Ulcerative colitis.
Slight aortic sclerosis.
Cysts of kidneys.
Weight of brain, 1250 grams.

Case 2 is a man whose mental trouble developed gradually at 63 and who died at 65, after one month in the hospital.

One aunt was insane. One of his four children died of convulsions. The family history was otherwise negative.

He was said to have had average mental ability and was of a cheerful temperament. All his life he had been addicted to excessive use of alcohol and had for over two years shown gradually increasing mental and physical failure with several attacks of hallucinatory delirium. One month before admission was said to have had a "shock" and to have been delirious and uncontrollable afterward.

On admission he was poorly nourished. Moist râles were heard over both backs. The heart was enlarged and arteries were thickened. Second aortic sound was loud and sharp. There were no murmurs. He walked with feeble, unsteady gait. There was fumbling in coordination tests. Hand grasps were feeble, right being slightly stronger. Knee jerks were very slight but equal. Pupils were equal and reacted normally. There was no history of lues.

He was feeble and remained in bed, showing no desire to rise. He was partially oriented. Speech was thick and indistinct. There was a fair memory for remote events but little for events from day to day. His spontaneous production was incoherent and rambling and vague, persecutory ideas were exhibited. Hallucinations were not pronounced. His emotional condition was unstable. He cried easily and was irritable. He gradually passed into a semi-comatose condition which lasted for a week before death.

The autopsy (five hours after death) showed the following conditions:

Hypostatic pneumonia with acute fibrinous pleuritis.

Slight aortic sclerosis.

Slight mitral sclerosis.

Marked sclerosis of cerebral vessels at the base.

Cardiac hypertrophy.

Chronic diffuse nephritis with cysts.

Chronic perisplenitis and pericholecystitis.

Sebaceous tumor of axilla.

Besides the marked basal arteriosclerotic changes, the intracranial tissues showed no other macroscopic signs of lesion, except a slight milkiness of the pia mater of the frontal region.

2. *Paranoic Conditions.*

Case 3 is a single woman whose insanity developed when 56-58 and who died in the hospital, aged 68, after eight years' hospital residence.

There was a history of neurotic and insane relatives. One brother was insane from early life. As a young woman she had excellent social and educational advantages and was considered a bright, capable woman. For two to three years before admission she had been suspicious, disagreeable and deluded.

Physical examination negative save for a systolic murmur at apex. Mentally she was oriented, showed good appreciation of surroundings. There was no pronounced deterioration. She fancied God talked to her and carried on conversation with Him, basing predictions, and prophecies upon what was said to her. Her delusions were of persecutory tinge, not systematized and related largely to religious and sexual matters. She was very repellent in attitude, keen and sarcastic in her comments. She was able to read and comprehend. Often she was profane and obscene in her talk and would be very disagreeable to some patients and unnaturally fond of others. There was no marked conduct disorder. There was a varying content to her delusions and a slowly increasing looseness of thought but to the last she was oriented and when annoyed would talk in keen, incisive and abusive manner. Two years before death weakness, numbness and tingling suddenly developed in right arm, and her writing, previously good, became illegible and her speech was thick but not aphasic. There was gradual improvement and no marked dementia following. Death occurred suddenly.

Anatomical Diagnoses.

Rupture of the heart wall due to infarction following thrombosis of posterior coronary artery.

Rupture of terminal branch of anterior coronary artery.

Hemopericardium with pressure upon lungs.

General arteriosclerosis (aortic, pulmonary (extensive), coronary, carotid, Circle of Willis, splenic, renal).

Sclerosis with calcification (thoracic aorta, coronary).

Hypertrophy of both sides of heart.

Slight chronic interstitial nephritis.

Chronic splenitis.

Multiple fibromyomata of uterus.

Slight cirrhosis of liver.

Chronic external adhesive pachymeningitis, more marked on left.

Slight chronic fibrous leptomeningitis (especially vertex and Sylvian regions).

Cysts of softening, right frontal cortex and of left side of pons.

Localized sclerosis of left precentral gyrus with induration of underlying white matter, most marked at junction of upper and middle thirds.

Slight focal cerebral atrophy (both Rolandic areas, left superior parietal lobule, olfactory bulbs and tracts, orbital gyri).

Slight marginal sclerosis of clival and cacuminal portion of cerebellum.

Calcified placques in pia mater.

Case 4 is a widowed woman aged 61 at admission. She was said to have been peculiar if not insane since the age of 50. Death occurred at 72 after 11 years in the hospital.

No family history obtainable. She had been a nurse. Persecutory delusions slowly developed accompanied by auditory hallucinations. She feared that men whom she heard about the house at night would kill her and kept a revolver for self-protection. The sexual element was prominent in her fears. At time of admission there was no marked deterioration. Auditory hallucinations were quite prominent for the first year or two but finally disappeared. Her delusions were not well systematized and she reacted by refusal of food, sullen, threatening attitude and occasional violence. There was considerable deterioration during last years in hospital. She became disoriented, careless of appearance and finally untidy. Her delusions became less prominent and her manner more agreeable. Several years before death she became mute, resistive, showed muscular rigidity, *Schnauzkrampf,* and refused food at intervals.

Anatomical Diagnoses.

General arteriosclerosis, with atheromatous ulcers, extreme in lower two-thirds of aorta and in coronaries (not so marked in visceral vessels) of but a few mm. in diameter.

Fatty myocarditis.

Chronic fibrous myocarditis.

Multiple cardiac infarctions.

Arteriosclerosis of coronary arteries with practically obliterated lumen.

Chronic diffuse nephritis of interstitial and arteriosclerotic type. (Very marked macroscopical changes.)

Cerebral arteriosclerosis, as far as secondary branches of Circle of Willis.

Cerebral atrophy, with focal sclerosis in left occipital and right parietooccipital regions.

Numerous small cysts of softening in both corpora striata and in right optic thalamus.

Diffuse atrophy of cerebellum with marginal sclerosis.

Absence of diploë.

Chronic external pachymeningitis.

Weight of brain, 1110 grams.

Case 5 is a widowed woman whose insanity began at the age of 66 and who died at 72 after five years' hospital residence.

Her father died of cardiac trouble and her mother of "Bright's disease." One brother committed suicide and two others were insane.

She had average mental capacity. No drug or alcohol habit. A year before admission she was said to have been overcome by heat and to have had a convulsive seizure, the only one noted. Nearly one year later she began to think people were plotting to kill her son and herself. She fancied electric wires were put under the floor to give her shocks, talking machines placed at her window to call her names and X-rays turned on her and that she had been hypnotized.

On admission she was a well-preserved woman for her age. She was perfectly oriented and had a good memory. Auditory hallucinations were active. She talked coherently. Protested against commitment, but admitted she had acted peculiarly. Her persecutory delusions were of sexual character and she was frequently disagreeable and repellent or abusive and denunciatory. For weeks at a time she would appear exhilarated and unusually active and then she would be moderately depressed in appearance and more tractable. There was no marked mental deterioration and she had good memory and was oriented up to time of death.

The autopsy (20 hours after death) showed the following conditions:

Hypostatic pneumonia.

Tumor of omentum with metastases in mesentery and peritoneum.

Fatty heart, liver and kidneys.

Ascites and edema of legs.

Calcified nodules in upper lobe of right lung.

Cholelithiasis with obstruction of cystic duct and distention of gall-bladder.

Chronic external adhesive pachymeningitis.

Cerebral atrophy of the convexity especially in frontal and parietal regions.

Case 6 is a single woman whose mental trouble began at about 60. She died at 77 after 7 years in the hospital.

Her father died of "apoplexy" and mother of "old age." One brother and one sister died insane. She had a good education and had been a woman of good habits, but had been regarded as eccentric and peculiar for 10 years. During the larger part of this time she lived alone. She became suspicious and finally exhibited to her relatives many persecutory and depressive ideas. She thought the Catholics were injuring her, that electric light flashes were used as signals by those in league against her. She heard voices and strange noises around her house. Finally she thought she was lost and unfit to meet her Maker.

On admission, she was poorly nourished, but aside from moderate peripheral arteriosclerosis, her physical health was good.

She was fearful and apprehensive in manner but perfectly oriented and keenly interested. Memory was excellent. At times she showed slight insight. She showed extreme apprehensiveness and thought she was being poisoned by Catholic conspirators. Was afraid of nurses and was greatly worried and distressed. A few days after admission she became mute, resistive, rigid and refused nourishment for a short time and showed the same symptoms some months later. She developed peculiar hypochondriacal delusions, based upon visceral sensations, thought she was going to be made a pauper and then left alone. Her persecutory ideas were constant. Memory and orientation were preserved to the last of her illness. There was never any psychomotor retardation.

Anatomical Diagnoses.

Malnutrition.

Tuberculosis of lungs with cavitation.

Sacral decubitus.

Edema of ankles.

Brown atrophy of heart.

Fatty heart.

General and coronary arteriosclerosis.

Chronic fibrous pericarditis.

Atrophy of liver.
Chronic nephritis with cysts.
Chronic splenitis.
Chronic adhesive pleuritis.
Chronic peri-appendicitis.
Cerebral atrophy and pigmentation.
Cerebral edema.
Edema of pia mater.

Intracranial vessels normal, except for dilatation and sclerosis of right posterior communicating artery.

Brain weight 1130 grams.

Case 7 is a widowed woman whose insanity was first recognized five to 10 years before death, which occurred at 75 after seven months in the hospital.

Her father died at 60, her mother at 90. No history of insanity or neurosis in family. Fairly capable woman. Had a family of three children. At age of 55 had an attack of inflammatory rheumatism and was taken to a city almshouse where she remained until transferred to the hospital, as she was crippled by rheumatism. For five to 10 years she had been deluded, suspicious and disagreeable.

On admission she weighed 76 pounds, fingers were contracted and joints enlarged and deformed. Nothing else of interest in physical examination.

She was quiet, orderly and neat in care of person. Orientation was perfect, her memory was good, school knowledge was retained, she had a good grasp on surroundings and fair knowledge of current events. Her productions were coherent. Auditory hallucinations were constant and were of abusive content. Her delusions were not systematized but were always persecutory in character and she talked about them freely. At times she was disagreeable in manner and would scold about her fancied abuses. She kept interested in surroundings and there was no pronounced mental deterioration at time of death.

Anatomical Diagnoses.

Bronchopneumonia.
Chronic diffuse nephritis.
Chronic passive congestion of liver.
Acute splenitis.
Chronic leptomeningitis.
Sclerosis of basal cerebral vessels.
Unequal pupils.
Chronic fibrous pericarditis (milk spot).
Scarring of apices of lungs.
Enlargement of retroperitoneal lymph nodes, slight.
Weight of brain, 1180 grams.

3. Delirious Conditions.

Case 8 is a man, who was 55 years old when admitted at Danvers.

His family history was not obtained. Friends stated that he had been a hard-drinking laborer who had never been insane. He had worked until a short time before admission.

There was no history of lues. He was poorly nourished. Urine showed cloud of albumin, sp. gr. 1024. Sediment contained broad and narrow hyalin casts, blood and pus corpuscles. The heart was much enlarged and second aortic sound was loud and sharp. He was feeble, tremulous, and unable to stand unassisted. There was no paralysis. Knee jerks were absent. Pupils were equal. Light reactions were not determined. There was a questionable history of specific lesion three years before.

He was completely disoriented. Attention could be held and he gave relevant replies. He reacted to visual and auditory hallucinations by feeble groping restlessness and broken, thick speech. No memory for recent events and that for earlier periods was fragmentary. At times he showed partial insight. There was no improvement. He took liquid diet freely. On the ninth day his rectal temperature which had previously been within normal limits fell to 91.4. Within 24 hours it slowly and gradually rose to 101.8. Physical examination showed nothing new. He became more feeble and stuporous and showed tendency to fabricate when aroused. He died on the 19th day after commitment.

Anatomical Diagnoses.

Small scar of penis.
Dilatation of pupils.
Emphysema of lungs.
Chronic adhesive pleuritis of both sides, posteriorly.
Moderate mitral sclerosis.
Moderate sclerosis of aortic arch.
Ecchymoses of fundus of stomach.
Chronic diffuse nephritis.
Aortic sclerosis with calcification of abdominal portion.
Calvarium shows little diploë.
Chronic external adhesive pachymeningitis.
Chronic fibrous leptomeningitis.
Marked edema of pia mater, posterior region.
Weight of brain, 1350 grams.

Case 9 is a man 56 years old, who had never shown mental symptoms until he was delirious following an acute otitis media six years ago.

One sister was said to be "peculiar" and another had "nervous prostration" in middle life. He was a man of fair ability, steady in habits and worked as a drug clerk for 32 years. Six years ago following his ear trouble he had inflammatory rheumatism and had not been well physically since then. He had not worked for two years. He became unreasonable in conduct and failed physically. Two weeks before admission he was unconscious for two hours and since then was "nervous and restless."

On admission he was well nourished. The urine showed cloud of albumin. Sp. gr. 1022. Sediment contained hyalin casts, leucocytes, and calcium oxalate. The heart was greatly enlarged. The second aortic sound was loud and second sound at apex was reduplicated. Arteries were thickened and pulse was irregularly intermittent. There was no paralysis. Hearing and vision were slightly defective. The pupils reacted promptly to light and knee jerks were equal and lively.

On admission he was imperfectly oriented. His school knowledge was imperfectly retained. Memory was greatly impaired and defects were covered by romancing. He constantly reacted to auditory hallucinations. He could not give any intelligible account of past events. There was an almost constant fumbling restlessness and he was untidy and feeble. He died nine days after commitment.

Anatomical Diagnoses.

Cardiac dilatation.
Acute myocarditis.
Hypostatic pneumonia.
Chronic perisplenitis.
Acute splenitis.
Acute bronchitis.
Obliterative fibrous pleuritis, right.
Aortic sclerosis.
Chronic external adhesive pachymeningitis.

Case 10 is a woman 55 years old who showed mental symptoms for the first time about five months before admission.

No family history was obtainable. She had been temperate. For six months or more she had suffered from kidney and heart disease.

On admission she was poorly nourished. There was general anasarca. Abdominal cavity contained fluid. Moist râles were heard over both backs. Heart was dilated, action was feebly intermittent, and sounds were fluttering and indistinct. The soft murmur heard could not be timed. The urine showed sp. gr. 1018, and contained albumin and hyalin casts. She was unable to stand. There was no paralysis. Knee jerks were equal and lively and pupils reacted promptly to light and were equal. There was great dyspnœa. She was completely disoriented and unable to recall recent events or to give any coherent history. She could not perform simple mental arithmetic. There was no insight. Visual and auditory hallucinations produced apprehensive reaction. She would beg for protection from those whom she thought would shoot or injure her. She made no effort to care for her person and was feebly restless until death occurred suddenly on the 12th day in hospital.

Anatomical Diagnoses.

General anasarca.
Cardiac dilatation.
Chronic passive congestion of liver, spleen, and kidneys.
Chronic diffuse nephritis.
Weight of brain, 1300 grams.

Case 11 is a man 70 years old who had showed no previous mental symptoms excepting two short delirious episodes within the past three years.

His father died of "rheumatism" at 80; his mother at 60 of unknown cause. A maternal aunt became insane at age of 50 and did not recover. Patient had been an industrious man of good habits. There was history of inflammatory rheumatism in early life and several milder attacks later. He had done no work for three to four years before admission. He had shown symptoms of present trouble for two months. When examined he was poorly nourished, limbs were edematous. Skin was dry and scaly. There was fluid in right chest. The heart was much dilated, arteries were thick, pulse was feeble and irregular, and a loud, musical systolic murmur was transmitted to the axilla. The urine showed sp. gr. 1022, 10 per cent albumin. Sediment contained broad granular and hyalin casts, pus cells and uric acid crystals. Neurological examination was negative. He was disoriented. Memory was gone for recent events, but at times he would exhibit fair recollection of early life. He could not write or perform mental arithmetic with any accuracy. At intervals he showed some insight. He became more restless and apprehensive and was totally unable to converse intelligibly and died in a few days.

Anatomical Diagnoses.

Focal sclerosis of basilar artery and of one Sylvian artery.
Cysts of softening in lower part of right centrum ovale external to tip of right lateral ventricle.

4. *Maniacal Conditions.*

Case 12 is a woman whose insanity developed at age of 52 and who died in the hospital at 69.

Both her parents died in extreme old age. One sister was peculiar from early life and considered insane, though never requiring commitment.

She had a normal development. At 25 she was married and had five children, one dying in infancy, another at the age of 23. The menopause occurred uneventfully at 40. From the age of 52 she was depressed or exhilarated, according to the history, much of the time. The attacks were not of regular duration. At one time she was well enough to live comfortably at home for three years. In her excitement she was loquacious disorderly, and elated. In the opposite condition she showed retardation, depression and difficulty in thinking. In both states she remained oriented until shortly before death and there was no marked dementia.

At time of admission, one year before her death, she was anemic and poorly nourished. Heart was slightly enlarged. Arteries were thickened. Urine, normal. Neurological examination was negative.

Her countenance was sad and she was apprehensive and bewildered. She remained in bed, moaning unintelligibly and was untidy. Answers to questions were usually in monosyllables and much of the time she was mute. For a few days at a time she would appear cheerful and talk volubly, showing a broken flight. At these times she would show fair memory and was oriented. For some months before her death she was untidy, depressed, retarded, and showed a tendency to self-accusation. She refused nourishment and failed slowly.

Anatomical Diagnoses.

Emaciation.

Hypostatic pneumonia with acute sero-fibrinous pleuritis, and (by extension) acute mediastinitis and pericarditis.

Small hemorrhages in gastric mucosa.

Acute splenitis.

Chronic diffuse nephritis.

General arteriosclerosis (aortic, coronary right anterior choroid, and pulmonary).

Chronic myositis with pigmentation (thorax).

Brown atrophy of heart muscle.

Mitral sclerosis.

Chronic fibrous endocarditis.

Chronic gastritis.

Chronic external adhesive pachymeningitis.

Chronic leptomeningitis (over sulcal vessels at vertex).

Deficiency in left vertebral and right posterior communicating arteries.

General encephalomalacia and myelomalacia.

Frontal, orbital, and central sclerosis.

Case 13 is a man who became insane at 63 and who died at 67 after two years' hospital residence.

His father died of pneumonia at 76 and his mother of tuberculosis at 28. A brother and sister also died of tuberculosis. There was no history of nervous or mental disorder in family.

He had been a hard-working farmer and made a good living for his family. He had been rather moody and quiet in temperament. Two years before admission he slowly developed an unreasonable attitude towards family, an increasing activity, a garrulous flight of expansive ideas and was sent to a private hospital. Then he became disorderly, destructive, and violent.

On admission he was in excellent physical condition. He had a keen, alert countenance. Orientation perfect and memory was excellent for recent and remote events. He had no hallucinations. There was no insight.

He talked incessantly for hours in the night simply to annoy others, which he would consider a great joke. He would write long abusive diatribes about the hospital, physicians, and nurses and announced his purpose of forming a league to reform hospitals. He would become so disorderly that seclusion was demanded and then the incident would be recorded as evidence and he would declare that his unbearable conduct was a part of his scheme. He was always coherent in talk and writing and his flight was orderly. Elation and psychomotor activity were constant. His conduct disorder was out of proportion to symptoms of intellectual impairment.

Anatomical Diagnoses.

Hypertrophy of heart.
Fatty heart.
Ascites.
Chronic external adhesive pachymeningitis.
Chronic fibrous leptomeningitis, especially along vessels.
Moderate basal arteriosclerosis.
Frontal cerebral atrophy.
Focal area of softening of paracentral lobule.
Weight of brain 1310 grams.
Ecchymoses of right hip and of right chest behind.
Multiple fractures of right humerus.
Hemorrhage of retroperitoneal tissue of right side.
Hemorrhage of retroperitoneal tissue about bladder and rectum, right side.
Emphysema and edema of lungs.
Emphysema of pleural adhesions and of mediastinum on right side.
Fractures of ribs, upper six ribs.
Fracture of right ilium and os pubis.
Hemorrhage of chest near attachment of hepatic ligaments.
Wound of right kidney.

Case 14 is a woman who suddenly became insane at the age of 57 and who died at 70 after 13 years in the hospital.

No reliable family history. She is said to have been well until a few weeks before admission when she became restless, talkative, and disorderly.

Her physical health on admission was good.

She was active, mischievous, irritable and disorderly. There was no marked deterioration. She was oriented. There was marked distractibility and her conversation was flighty and broken. Excepting for short outbreaks of irritability she was constantly elated. The condition was constant to the end.

Anatomical Diagnoses.

Marked emaciation.
Sacral decubitus.
Bronchopneumonia.

Interstitial nephritis.
Chronic fibrous myocarditis.
Chronic passive congestion of spleen, and chronic perisplenitis.
Varicose veins of legs.
Chronic endocarditis, mitral and tricuspid.
Ascites.
General tubercular peritonitis.
Tuberculosis of intestines.
Tuberculosis of liver.
Tubercular adenitis of peri-bronchial lymph nodes.
Sinus into right knee joint.
Chronic patellar bursitis, right.
Superficial wound of left thigh.
Sub-acute cholecystitis.
Chronic external adhesive pachymeningitis.
Weight of brain, 1110 grams.
Chronic obliterative pleuritis, right.

5. *Depressed Conditions.*

Case 15 is a man aged 58 who showed first evidence of mental trouble at 56 and who died at 58, after four months' in the hospital.

His father died of apoplexy at 70, and mother at 80 of unknown cause. No history of neurosis, psychosis or intemperance in his family.

He never used alcohol, and had been a hard-working man of frugal habits. For two years before admission, he had exhibited an increasing hypochondriacal depression. Twice he had persuaded surgeons to perform an exploratory laparotomy, to no effect. He became more restless, agitated and suicidal and was committed.

On admission, he was poorly nourished. Heart was enlarged, arteries moderately thickened, pulse feeble, sounds were very faint. Urine contained a trace of albumin and was otherwise normal. Neurological examination was negative.

His expression was sad and hopeless. He was constantly groaning and talking volubly. Orientation was perfect and memory was not impaired. No hallucinations observed. He talked freely about his feelings of unreality and nihilistic ideas. The following excerpts show their character:

"There it is. I am all ablaze. I am burning, burning. Every breath that comes out of my mouth is as hot as if it were coming from a steam-engine. I burn just like a fire. It must be Hell. I will last as long as the earth. My God, man, look here. I am all afire. Oh, burning, burning, and I can't take water. Water don't check my thirst. I tell you one thing, when you talk to me, you are talking to Hell. I am craving for nuts, apples, milk, everything, and I can't take them. I've got no stomach and it is no use to put them in my mouth. I am in Hell. I am all afire. This will never take my life. Oh, this is pain. It biteth like a serpent and stingeth like an adder. You can shoot me full of bullets and I won't die. My spirit sticks my throat together. I would give a million dollars if I had a disease which would kill me. Everybody will be dead and gone, the world will have passed, these trees will be gone and this building will be rotted down and I will still be here."

Aside from physical failure, there was little change in his condition before death.

Anatomical Diagnoses.

Pulmonary tuberculosis, small old focus.
Pulmonary hypostasis, slight.
Chronic diffuse nephritis.
Slight aortic and coronary sclerosis.
Weight of brain, 1370 grams.

Case 16 is a widowed woman about 65 years old, whose mental trouble began about six months prior to death, which occurred after three months in the hospital.

Her father died at 75 of rheumatism her mother at 73 of pneumonia. One brother died insane and the family history was otherwise negative.

She was a mill operative and nurse before marriage, at 46. Menopause occurred uneventfully, at 50. For some months, she had been nursing an invalid husband, who died. She became depressed, restless and came to the hospital as a voluntary patient.

She was fairly well nourished. Heart was slightly enlarged. Arteries were thickened and there was a well-defined arcus senilis. Pulse regular; second aortic sound was sharp and clicking. Urine showed hyalin casts and albumin. Aside from subjective sensations, neurological examination was negative.

She was much depressed, sleepless and agitated. Orientation was perfect at first and school knowledge was retained. Memory for early events was good, but somewhat impaired for recent periods. Auditory hallucinations developed and voices of her family were heard, later she saw people who had been raised from the dead. Her attention and memory showed more impairment and feelings of unreality developed and she talked about them constantly.

"Oh dear. Why don't they do something so I won't suffer. See my legs and see my eyes. I am turning into an animal. Blotches have come on my skin, it is all shrunk up and my eyes look fierce like a squaw's eyes. Send me home, I can't stand it. Why can't you put something through me to kill me. Oh, my God. I've got to be like a bear. Why am I so crazy? Oh, dear. Why am I to be killed?"

For short periods, her attention could be held and she had partial insight, but she grew rapidly worse, becoming less communicative and refusing food before death.

Anatomical Diagnoses.

Nutrition poor.
Surgical incisions of right forearm, left forearm and right knee.
Slight coronary arteriosclerosis.
Slight sclerosis of aortic arch.
Fatty liver.
Hyperemia of spleen.
Slight edema of lungs.
Chronic interstitial nephritis.
Smooth globular, subcapsular encapsulated tumor of right kidney.
Submucous fibromyoma of uterus.
Subperitoneal fibromyoma of uterus with calcification.
Polyp extending from the upper wall of uterus to vagina.
Slight chronic external adhesive pachymeningitis.
Focal sclerosis of right Sylvian artery (one patch).
Weight of brain 1220 grams.

Case 17 is a man who first became insane at 65 and who died within six months.

His father died at 77 of cardiac disease and his mother at 67, after three years of senile dementia.

He served in the Civil War and for 35 years had worked as an operative. He was a man of pleasant disposition and industrious and temperate habits. When 61, he had grippe and typhoid fever. Was delirious during both illnesses. He worked steadily until nine weeks before commitment, though he had been sleeping poorly, losing weight and exhibiting depression for some weeks. He fancied that his family would starve and freeze, that he was decreasing in size, and that others were growing larger. He refused nourishment.

On admission, he was emaciated. Heart was not enlarged; second aortic sound was loud. Pulse was feeble and arteries were soft. There was a faint arcus senilis. The urine contained no albumin or casts. Reflexes were equal and lively. Muscular movements were well performed. There was no history of lues.

He was oriented for time, place and persons and showed good memory. School knowledge was well retained though answers to tests were given accompanied by protestations that he could not tell, that he had no brains, etc. He talked sharply in almost petulant manner, though showing depression and agitation. His spontaneous productions are shown by the following:

"I've got no brains and I can't talk and you are going to make out a wrong report. I've got no heart and no stomach and I can't swallow. I haven't any feelings." At another time, when addressed, he said: "Yes, you are all great big men and so strong, you must weigh over 400 pounds, and I am so small you can't see me. I'm freezing to death and you cover me with great heavy blankets. I would not burn if you threw me in the hottest furnace, but I can't suffer because I have no brains."

He refused food and failed rapidly, showing similar symptoms to the end.

Anatomical Diagnoses.

Nutrition poor.

Chronic adhesive pleuritis of both apices.

Thrombosis of right auricle.

Bronchopneumonia of both lower lobes.

Embolism of primary branches, of left pulmonary artery.

Chronic perisplenitis.

Suppuration of retroperitoneal tissue (pneumococcus and other bacteria), probably due to thrombosis of left renal veins.

Pyelitis.

Ureteritis.

Cystitis.

Vesiculitis.

Moderate aortic sclerosis.

Thrombosis (3 x 2 x 1 cm.) of aorta.

The above case has been previously reported in full by Mitchell and Southard, Melancholia with Delusions of Negation: Three Cases with Autopsy, *Jour. Nerv. Mental Disease,* May, 1908.

Case 18 is a married woman, whose first mental trouble occurred two months prior to death, at 58, three weeks after admission to hospital.

Her father died of tuberculosis at 68, and her mother in middle life of some intestinal trouble. Four brothers and sisters alive and well. No history of neurosis, psychosis, or intemperance in family.

She was of a bright, cheerful temperament and was married at 28. She had no children. The menopause occurred uneventfully at 49. Her mental trouble began with worry, sleeplessness, feeling of poverty, hallucinations and development of depressive persecutory ideas.

On admission, she was poorly nourished. Heart was not enlarged. Arteries were thickened. Pulse was small. Urine showed albumin and hyalin casts. Tendon reflexes exaggerated.

She was apprehensive and inactive. There was little spontaneous speech though she moaned and sighed. Orientation was imperfect, but her memory was good. Attention was held with difficulty. Questions were answered after initial delay of 10 to 30 seconds.

Q. "Are you afraid?"

A. "Yes, of everything."

Q. "What makes you afraid?"

A. "Oh, I don't know, lots of things. I am afraid something is going to happen to me."

Q. "Why can't you stay in bed?"

A. "Because I am afraid."

Her depression and restlessness increased but the character of her productions remained unchanged until death.

Anatomical Diagnoses.

Acute enteritis, in places diphtheritic.
Bronchopneumonia, slight.
Chronic diffuse nephritis.
Thrombosis of branch of right middle cerebral artery.
Chronic fibrous pleuritis.
Cysts of choroid plexus.
Aortic sclerosis.
Weight of brain, 1330 grams.

Case 19 is a man whose mental trouble first developed at 70. He died at 71 after eight months in the hospital.

The family history was negative. He had used liquor freely until within a few years but not sufficiently to produce recognized mental symptoms. For about one year, he had been depressed and after, threatened suicide. Finally he cut his throat and was committed one week later. During this period, he was said to have been "clear and rational," excepting on a few occasions when he appeared unusually disturbed and showed suicidal tendencies.

On admission, he was pallid and poorly nourished. There was a suppurating, superficial wound. There were moist râles and dulness at both apices. Heart was not enlarged. Arteries were hardened and arcus senilis was marked. Urine contained a few hyalin casts, but no albumin.

He appeared depressed. Talked responsively in low, soft tones with some delay and few words. He was fairly well oriented. There was slight memory impairment for both recent and remote events. He was not hallucinated. Partial insight was displayed and he was thankful that the suicidal attempt was unsuccessful. He showed ill-defined persecutory ideas and worried about his family relations, but showed no peculiar reaction to his surroundings. His depression was constant and he became more reticent. He was always orderly in conduct and neat in habits. Death occurred after gradual physical failure.

Anatomical Diagnoses.

Marked emaciation.
Scar of neck at upper border of cricoid cartilage.
Chronic fibrous pleuritis, left.
Chronic obliterative pleuritis, right.
Milk patch of left ventricle and left auricle.
Slight mitral sclerosis.
Abscesses of right apex.
Chronic tuberculosis of lungs with acute fibrinous pleuritis of right lung.
Diverticula of descending colon.
Chronic perihepatitis of left lobe.

Scars of kidneys.
Hernia of left side of bladder.
Chronic external adhesive pachymeningitis.
Basal cerebral arteriosclerosis.
Focal cerebral atrophy (opercular region).
Chronic internal hydrocephalus.
Weight of brain, 1240 grams.

Case 20 is a man whose mental trouble began at 52 and who died three months later, after two weeks in the hospital.

Insanity and intemperance in the family were denied.

He had been a capable bookkeeper of rather eccentric manner and solitary habits. He was not intemperate. Following hard work and some business worry, he tried to throw himself in front of a moving train a month before his admission. For a few days he was excitable and depressed but soon improved. He heard voices talking to him and he was committed.

He was poorly nourished. Physical examination was negative, excepting inequality of knee jerks. Urine was normal.

His movements were feeble and his expression worried, and apprehensive. He talked slowly, after making long pauses; voice was low and indistinct. He was partially oriented. Memory for recent and remote events good. He had a good appreciation of surroundings. Auditory hallucinations were prominent and of frightful content and were reacted to by fear and apprehension. He was self-condemnatory; blamed himself for the many losses of his employers; thought he would communicate disease to those about him. He wanted to die as there was no hope for him. He showed restless agitation, would not remain in bed; refused proper food and became uncommunicative before death.

Anatomical Diagnoses.

Marked emaciation.
Dilatation of pupils.
Chronic fibrous pericarditis.
Aspiration pneumonia with acute fibrinous pleuritis.
Old scars of right kidney.
Chronic perihepatitis with adhesions to peritoneum.
Chronic peri-appendicitis.
Enlargement of mesenteric lymph nodes.
Adhesions of scalp to calvarium.
Marked chronic external adhesive pachymeningitis.

Case 21 is a man whose depression was first observed at 51 and who died at 54 after two years' hospital residence.

His father was living. His mother was neurotic and died of consumption at 58. One maternal uncle was an imbecile, another was intemperate. One brother was neurasthenic and intemperate.

He had average ability, was industrious and temperate. His manner was quiet and reserved and he was inclined to worry over trifles. For two years he had had financial trouble and for six months had been depressed and shown a tendency to self-accusation and had been afraid he would injure family or himself.

On admission, he was pallid and emaciated. There was evidence of pulmonary tuberculosis. Heart was enlarged and there was a thrill and presystolic murmur at the apex. No history of lues. Urine was normal. Inequality of knee jerks was the only thing of interest in neurological examination.

His expression was sad and dejected and his movements were slow and feeble. Orientation was perfect and memory was unimpaired. Auditory hallucinations were noted. He said his conscience talked to him, once remarking, " It is a mockery for me to pray, and when I try, my conscience goes to work and gives me such a wild feeling I don't know what to do." Later, he heard voices of his relations calling to him and saw faces. He blamed himself and thought he had sinned unpardonably and caused others to suffer. Fancied he could see fire and smoke rising from Hell and that he heard the voice of God summoning him to appear and take his punishment. He rarely took the initiative in talking. His voice was low and indistinct. He was neat and orderly in conduct. Three months before death, a tubercular mediastinal abscess was drained. He failed physically and his depression, hallucinations, apprehensiveness, and self-accusation remained unchanged. Memory and orientation good to the end.

Anatomical Diagnoses.

Pulmonary tuberculosis, far advanced on both sides, with cavitation and caseation.

Chronic tuberculous pleuritis.

Anomaly of left olfactory tract.

Marked emaciation.

Operation wounds on anterior aspect of chest.

Subcutaneous sinus on left aspect of chest.

Arteriosclerosis of coronaries and of aorta, slight.

Chronic passive congestion of liver.

Weight of brain, 1410 grams.

Case 22 is a woman who was well until age of 55 and who died at 59 after four years in the hospital.

Her mother died of " softening of the brain " at 75, and her father at 50 of unknown cause. One paternal cousin was insane. Three brothers and sisters in good health. She was married at 19 and had one living child. Menopause occurred uneventfully at 40. She never had any serious illness. For two months, before admission, she was restless and showed increasing agitation, pacing to and fro, picking at her clothing, whispering to herself. She exhibited self-depreciation, cried and talked of suicide.

When admitted, she was emaciated. There was a slight peripheral arteriosclerosis. Heart was not enlarged. Urine contained albumin and granular casts.

She presented an appearance of dejection, talked in a low, almost indistinct tone. There was little motor activity. She would sit for hours in contracted attitudes and occasionally pace slowly about in aimless manner, wringing her hands and moaning. Orientation was perfect and memory was good. Auditory hallucinations were transitory. Her attention could not be diverted and she had distressing delusions; imagined that she had a loathsome disease, that she had been a wicked woman, that a terrible fate had overtaken her relatives. Distressing nocturnal, visual hallucinations developed and her condition is well shown by an occasional outburst. "I am under a terrible influence. I can't help it. If I only could see things as you do. I have done wrong. I was born under a curse. I didn't know my mother was diseased until I came here. I know I have got the bad disorder. I am not going to eat any more. I don't want to live. Please don't do anything for me, doctor, I want to die, but I don't want to be tortured to death. Can't you let me die quickly?" She became more depressed and retarded; would rarely speak spontaneously, except to beg that she might die. She would attempt to empty her stomach after forced feeding. She was oriented and had fair memory until her death.

Anatomical Diagnoses.

Edema of left hand.
Acute purulent pericarditis.
Slight chronic fibrous pleuritis, posteriorly.
Hydropericardium.
Brown atrophy of heart.
Hypertrophy of heart.
Bilateral bronchopneumonia.
Liver weight, 760 grams.
Renal atrophy.
Moderate aortic sclerosis.
Weight of brain, 1040 grams.

Case 23 is a man who developed a depression at 64, attempting suicide, made a fair recovery and died at the hospital eight years later.

His family history was not obtainable.

He had used liquor freely in early life but had never been insane and for 10 years had been temperate. For some months, prior to admission, he had been very despondent and unable to work. He filled his pockets with rocks and jumped into the river. After being rescued, he was brought to the hospital. At that time he was considered to be a case of "acute melancholia." It appears from the incomplete record, that he recovered in a few months. He was a good machinist and desiring to remain at the hospital, he was allowed to work for a small compensation and for eight years prior to death, he showed no evidence of mental derangement.

The autopsy (three hours after death) showed the following conditions:

Carcinoma of stomach with secondary nodules in liver.
Miliary tuberculosis of peritoneum and parietal pleura.
Emaciation.
Anemia.
Chronic obliterative pleuritis, left lung.
Chronic adhesive pleuritis, left apex.
Fibrous aortitis about origins of intercostal arteries.
Slight chronic fibrous leptomeningitis.

III. CLINICAL SUMMARY.

In this summary we have included some general statistical features, but have paid special attention to the diagnostic points which tend to separate these cases from arteriosclerotic and senile atrophic cases.

Sex.

There are 12 male, 11 female patients in our series. Both alcoholics were male. The five paranoics were female. Three of the delirium cases were male, one female. Two of the maniacal cases were female, one male. Six of the depressed cases were male, three female. If the maniacal and depressed cases are placed in one group, there are seven male cases, five female.

Hereditary Factors.

Hereditary factors may be excluded (with the usual reservations for these State hospital patients), in Cases 1, 7, 13, 15, 18, 19, 20; occur but are not especially prominent in Cases 2, 9, 11, 12, 16, 17, 22; are well marked in Cases 3, 5, 6, 21; and are impossible to affirm or deny in Cases 4, 8, 10, 14, 23.

A decision concerning these factors is obviously rendered difficult by the age of the patients and the dispersion of parental acquaintances.

The group of cases with hereditary factors not prominent contains "one aunt insane" (Case 2), "peculiar sister" and "sister with nervous prostration" (Case 9), "maternal aunt insane at

50" (Case 11), "peculiar sister" (Case 12), "brother insane" (Case 16), "mother senile dement three years" (Case 17), "paternal cousin insane" (Case 22). In the group with marked hereditary factors, including Case 3 (neurotic and insane relatives, brother insane), Case 5 (two brothers insane, third a suicide), Case 6 (brother and sister insane), Case 21 (mother neurotic, one maternal uncle imbecile, another intemperate, brother neurasthenic and intemperate), all cases appear to show the probability of hereditary factors emerging in brothers or sisters of the patients in question.

Hereditary factors of more or less importance are present in 47 per cent of the series as a whole, or in 74 per cent of those cases in which reliable histories were obtainable.

Antecedent Factors.

Alcoholism of excessive grade appears to play a part in two cases (1 and 2), possibly also in three more (8, 19, 23), all male cases.

Arteriosclerosis was clinically recognizable in 10 cases, including the following (with age at examination):

2 æt. 65, 6 æt. 70, 9 æt. 56, 11 æt. 70, 12 æt. 68, 15 æt. 58, 16 æt. 65, 18 æt. 58, 19 æt. 70, 22 æt. 55 (slight). Of these cases two only (Cases 2 and 19) gave clinically recognizable arteriosclerosis *together with* a history of excessive alcoholism.

Heart disease was clinically recognized in nine cases (2, 8, 9, 10, 11, 12, 15, 16, 21).

Kidney disease was clinically recognized in nine cases (8, 9, 10, 11, 15, 16, 18, 19, 22).

Heart and kidney disease combined occurred in six cases (8, 9, 10, 11, 15, 16).

Arteriosclerosis, heart disease, and kidney disease combined occurred in four cases (9, 11, 15, 16).

Inflammatory rheumatism is prominent in two histories (7, 11); "grippe and typhoid fever" four years before onset, Case 17; otitis media followed by delirium, Case 9.

Of social factors, business troubles appear in Cases 20 and 21, exhaustion by nursing, Case 16.

Age at Onset and Duration.

		Age at Onset.	Age at Death.	Duration.
1.	M.	57	63	6 y.
2.	M.	63	65	2 y.
3.	F.	56-8	68	10-12 y.
4.	F.	50	72	22 y.
5.	F.	66	72	6 y.
6.	F.	60	77	17 y.
7.	F.	65-70	75	5-10 y.
8.	M.	55	55	brief.
9.	M.	50	56	6 y.
10.	F.	55	55	5 m.
11.	M.	67	70	3 y.
12.	F.	52	69	17 y.
13.	M.	63	67	4 y.
14.	F.	57	70	13 y.
15.	M.	56	58	2 y.
16.	F.	65	65	6 m.
17.	M.	65	65	6 m.
18.	F.	58	58	2 m.
19.	M.	70	71	1 y.
20.	M.	52	52	3 m.
21.	M.	51	54	3 y.
22.	F.	55	59	4 y.
23.	M.	64	72	8 y.

Character of Onset.

The onset was gradual in Cases 1, 2, 3, 4, 6, 7, 10, 12, 13, 15, 16, 17, 19, 21, 22, 23—sixteen cases.

The onset was sudden in Cases 5, 8, 9, 11, 14, 18, 20—seven cases.

Both alcoholics, four of five paranoic cases, one of four delirious cases, two of three maniacal cases and seven of nine depressed cases had a gradual onset.

One of five paranoic, three of four delirious, one of three maniacal, and two of seven depressed cases had a sudden onset. Brief characterizations of onset are:

1. Business failure due to growing amnesia and fabrications.
2. Gradual mental and physical failure, hallucinatory attacks.
3. Unsystematized persecutory, religious and sexual delusion formation.

4. Unsystematized persecutory sexual delusions and auditory hallucinations.

5. Single convulsive seizure ("overcome by heat"). Persecutory delusions one year later.

6. Eccentric and peculiar, persecutory delusions, depressive ideas, auditory hallucinations (?).

7. Persecutory delusions, auditory hallucinations.

8. Unknown. Physical weakness. Visual and auditory hallucinations.

9. Delirium following otitis media, inflammatory rheumatism, physical failure, amnesia, fabrication, unreasonable conduct.

10. Cardiorenal disease.

11. Delirious episodes.

12. Depression and exhilaration in attacks of irregular duration.

13. Slowly developing unreasonable attitude.

14. Psychomotor excitement.

15. Increasing hypochondria.

16. Restless depression while nursing husband.

17. Insomnia, loss of weight, depression.

18. Insomnia, worry, feeling of poverty, hallucinations, persecutory delusions.

19. Depression and suicidal threat.

20. Hard work and business worry.

21. Financial trouble, self-accusations.

22. Psychomotor excitement with depressive ideas.

23. Despondency and suicidal attempt.

General Clinical Features.

The signs of *peripheral* motor or sensory *disorder* were very few in this series. Case 9 (with defective hearing and vision) was the only case of sensory disorder at all marked. Case 1 showed sluggish pupillary reactions and diminished knee jerks. Case 2 showed ataxia and diminished knee jerks. Case 8 showed knee jerks absent; Case 18, knee jerks exaggerated; Cases 20 and 21, knee jerks unequal.

There are also few instances giving evidence of *focal brain lesion.* Case 3 developed weakness of one arm, with difficulty in writing and thick speech eight to 10 years after onset of mental disease and two years before death. Case 2 is said to have had a "shock" one month before admission, two months before death. Case 5 is said to have had a convulsive seizure at 65, six years before death. Case 9 is described as having an attack of unconsciousness 23 days before death, followed by nervousness and restlessness.

Hallucinatory disturbances form a feature in 13 of the 23 cases (56 per cent), purely auditory in eight cases (3 (?), 4, 5, 6, 7, 9, 18, 20) and auditory combined with visual in five cases (8, 10, 16, 21, 22). In the other cases, naturally, hallucinations may have been present, but are uncertain. The auditory hallucinations of Case 4 disappeared after two years. Those of Case 18 were features of the onset only.

Delusions characterized, in addition to the five paranoics (3, 4, 5, 6, 7), also Cases 2, 12, 15, 16, 17, 18, 19, 20, 21, 22, that is in 15 cases (65 per cent). Twelve of these showed allopsychic delusions, of which seven (2, 3, 4, 5, 7, 18, 19) showed such delusions in a comparatively simple or uncombined form (delusions of persecution), three (15, 16, 17) showed them commingled with various autopsychic and somatopsychic delusions of a metaphysical sort (feelings of unreality and nihilistic ideas), one (4) developed visceral delusions in addition to allopsychic, and one (21) showed a slight admixture of allopsychic delusions with self-accusatory ones. Three cases (12, 20, 22) show self-accusatory delusions in comparatively pure form. The persecutory delusions in three female cases (3 æt. 56-8 at onset, 4 æt. 50 at onset, 5 æt. 66 at onset) had a sexual tinge. Cases 3 and 6 showed delusions of a religious character. In Case 18 there was onset with worry, insomnia, feeling of poverty, and persecutory ideas; but in the hospital the picture changed or developed into a state characterized chiefly by fear.

Amnesia for recent events characterized Cases 2, 11, and 16 (slight); for both recent and remote events, Cases 1, 8, 9, 10, 19 (slight). Attempts to supply the gaps in memory by fabrications characterized 1, 8, and 9; two of these cases (1 and 8) had alcoholic histories; but the third (9), a drug clerk for 32 years, was a man of originally fair ability and steady habits.

Disorientation in greater or less degree marked the course of eight cases (1, 2, 4 (late), 8, 9, 10, 11, 18), that is in all the cases provisionally called "delirious" (8, 9, 10, 00), in 1 and 2 (alcoholic dementia), 4 (of late development in a case with much cerebral arteriosclerosis and atrophy), and 18 (orientation neglected through absorption by fear?).

Seven of the 23 cases could perhaps be placed in the manic-depressive group. Cases 5 and 12 had attacks of exhilaration and depression. Case 14 remained in a constant elation with psychomotor restlessness, distractibility, flight of ideas and words, for 13 years, till death at 70. Cases 18, 20 and 22 showed depressions, characterized by retardation. Case 23 recovered from his single attack of depression with suicidal attempt at 64, was employed at the hospital as machinist, and died at 72 of tuberculous peritonitis.

Katatonic features were strikingly rare. Two cases of the "paranoic" group (4 and 6) at times showed katatoniform signs which were possibly, however, merely reactive to delusions.

Suicidal ideas were expressed by 15, 21, 22, and *attempts* were made by 19, 20, and 23.

IV. Anatomical Summary.

As bearing upon the relation of these cases to cases of arteriosclerotic brain disease and of senile atrophy, an analysis of the vascular and cardiac findings in this series is especially important. To this we have added the renal findings.*

Four cases (3, 4, 6, 12) showed extensive *general arteriosclerosis.* There was more or less aortic *sclerosis* in 18 cases out of 23. This sclerosis was marked and associated with calcification or ulceration in four cases (3, 4, 8, 9), moderate in five cases (6, 12, 18, 22, 23), slight in eight cases (1, 2, 5, 10, 15, 16, 17 (thrombus), 21), and presumed on collateral evidence (no note made) in one (11). Aortic sclerosis was absent in five cases (7, 13, 14, 19, 20).

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* In the correlation of these we have been aided by Dr. E. T. F. Richards, working at the Danvers Hospital under the Proctor Fund of Harvard University.

Arteriosclerosis elsewhere than in the aorta was noted in 12 cases (2, 3, 4, 6, 7, 10, 11, 12, 13, 15, 16, 21). Of these 12, three cases (10, 15, 21) showed a coronary sclerosis, four showed basal cerebral arteriosclerosis (2, 7, 11, 13), and one (16) showed coronary and cerebral (Sylvian) sclerosis.

Three cases (14, 19, 20) showed no sign of arteriosclerosis, two (7, 13) showed cerebral without general or aortic sclerosis, eight (1, 5, 8, 9, 17, 18, 22, 23) showed aortic without other arteriosclerosis.

Considering next the heart, we find *hypertrophy* of the left ventricle in four cases (2, 3 (also right), 5 (also right), 13). It is to be observed that Case 5 showed only slight aortic sclerosis and Case 13 showed only cerebral arteriosclerosis.

Chronic *interstitial myocarditis* occurred in four cases (4, 10, 14, 23), pronounced brown atrophy in three cases (10, 12, 15).

The *valves* are noted as normal in nine cases (6, 7, 8, 9, 13, 15, 16, 17, 18, 21), showed slight changes, largely mitral, in 11 cases (1, 2, 3 (aortic stiff and calcified), 4, 5, 8, 10, 12, 14 (tricuspid and mitral), 19, 23). The valvular conditions are not noted in three cases (11, 20, 22).

Case 3 showed rupture of heart due to thrombosis of coronary artery; Case 4 showed multiple cardiac infarctions; Case 17 showed a right auricle thrombus; and Case 22 showed marked hydropericardium.

The *kidneys* showed *chronic lesions* in 21 out of 23 cases (*i. e.*, except in 5 and 23). But these lesions were slight in 10 cases (1, 2, 3, 8, 9, 17, 19, 20, 21, 22), leaving 11 cases with anatomically marked lesions, (Case 11 is deficient in notes, but is presumed from other evidence to have shown marked lesions). Of these 11, 4 cases showed lesions of the chronic interstitial type (Cases 6, 13, 14, 16), and eight cases showed lesions of the chronic diffuse type (Cases 4, 7, 10, 12, 15, 18), and one case (11) was undetermined.

It is noteworthy that the cases of marked general arteriosclerosis are not those which showed cardiac hypertrophy (except Case 3) but that three of the general arteriosclerotic cases (4, 6, 12) showed well-marked renal lesions.

The brains in order of weight are:

Male.		Female.	
Case No.	Weight.	Case No.	Weight.
19	1240	22	1040
1	1250	4	1110
13	1310	14	1110
23	1310	6	1130
8	1350	12	1135
15	1370	7	1180
21	1410	16	1220
2	1430	10	1300
		18	1330
		3	1365

The weights in 5, 9, 11, 17, 20 are not recorded; there is reason to believe that Cases 5, 11 were atrophic and that Cases 9, 17, 20 weighed within normal limits (see microscopic notes under casuistic summary).

V. Casuistic Summary.

The main clinical and anatomical features, together with histopathological notes, concerning each case have been gathered for convenience in this section. The details of the microscopic examination have been largely omitted.

Emphasis has been laid chiefly on the distribution of pigmented substances in (1) the cells of the perivascular spaces, (2) the neuroglia cells (including satellite cells), and (3) the nerve cells. The pigment referred to is, as a rule, not the yellow pigment occurring as unilocular masses in senile nerve cells, but a more diffuse brownish granular or irregular pigment which when it occurs in nerve cells, is of more general distribution in the cell body. Six or more blocks, representing three or more areas (usually superior frontal, precentral, and occipital) in each hemisphere, were examined in Heidenhain iron-hematoxylin or Marchi preparations along with Nissl sections from the same regions.

Case 1, male, alcoholic, at 57 failed in business, became amnesic, fabricating, disoriented, with sluggish pupils and diminished knee jerks, and died at 63 from ulcerative colitis. Slight aortic sclerosis. Valvular endocarditis. Brain weight, 1250 grams. Considerable subpial gliosis. Moderate perivascular cell pigmentation throughout. Neuroglia cell pigmentation everywhere considerable, but extreme in precentral and calcarine regions. Satellite cell pigmentation in the layer of medium-sized pyramids and in lower layers of frontal region; characteristically about the Betz cells, but also elsewhere in the cell layers of the precentral gyrus. It is noteworthy that in many instances, though not constantly, the satellite cells are deeply pigmented and at the same time lie adjacent to non-pigmented cells or to cells containing senile yellow pigment masses which fail to stain by the iron-hematoxylin method. The nerve cell pigmentation differs in the three areas. The major pigmentation in the frontal region is found in the layer of medium-sized pyramids and in the layer of large external pyramids; in the latter layer are some instances of what is possibly true pigmentary degeneration (a process, somewhat rare, leading to cell destruction). In the precentral gyrus the Betz cells show intense pigmentation by the iron-hematoxylin method; among these are some instances in which senile yellow pigmentation occurs. In the calcarine cortex it is surprising to find, in view of the marked Betz cell pigmentation of the precentral gyrus, that the solitary cells of Meynert are comparatively free from such pigment. The frontal cortex in this case shows some numerical loss in the layer of small pyramids.

Case 2, male, alcoholic, at 63 began to have attacks of hallucinatory delirium, "shock" (?) two months before death, peripheral arteriosclerosis, speech thick, amnesia for recent events, vague persecutory delusions, emotionally unstable. Coma one week before death. Death from hypostatic pneumonia. Chronic diffuse nephritis. Slight aortic sclerosis. Marked basal cerebral arteriosclerosis. Cardiac hypertrophy. The lower layers of the cortical areas examined show considerable neuroglia cell pigmentation, and the external pyramidal cells are maximally affected by pigmentation. But there is little sign of lesion in the outer cortical layers, except a slight subpial gliosis in the frontal region (there was a slight milkiness of the overlying pia mater grossly observed). Perivascular cell pigmentation moderate.

Case 3, female, developed persecutory delusions of a religious and sexual cast at 56-8, at 66 developed weakness, numbness and tingling in right arm, difficulty in writing, and thickness of speech, recovered from this attack with slight dementia, and died from rupture of the heart at 68. This case showed the most pronounced general arteriosclerosis in the whole series. There is great probability, however, that this was developed, at least in great measure, after the development of the mental disease. Attention may be called to the curious localized sclerosis at the junction of the left precentral gyrus with induration of the underlying white matter: it is probable that this is related with the right arm symptoms just noted (cf., however, also pontine cyst).

Interpretation of microscopic findings is difficult on account of the complicating arteriosclerosis; but inspection of areas, remote from cysts of softening, shows a moderate nerve cell pigmentation and considerable neuroglia and perivascular cell pigmentation of quite general distribution.

Case 4, female, peculiar after 50, slowly developed sexual persecutory delusions, had auditory hallucinations which disappeared after 63, gave less evidence of delusions in later years and showed some katatoniform signs. Death at 72 from multiple infarctions of the heart. General arteriosclerosis was well marked. There were numerous areas of cortical sclerosis as well as cysts of softening in corpora striata and right optic thalamus. In connection with the katatoniform movements, attention may be drawn to a diffuse cerebellar atrophy with marginal sclerosis. The microscopic examination showed, in addition to arteriosclerotic changes, neuroglia and nerve cell pigmentation of a non-characteristic distribution, with moderate perivascular cell pigmentation.

Case 5, female, had a somewhat questionable convulsive seizure at 66, developed gradually at 67 persecutory delusions of sexual and religious character with auditory hallucinations, in hospital showed weeks of exhilaration followed by weeks of depression, showed at no time either amnesia or disorientation, and died at 72 of hypostatic pneumonia, fatty heart, liver, and kidneys, and multiple abdominal tumors. The brain showed atrophy, notably in the frontal and parietal regions. The microscopic examination showed far fewer changes than the gross observations would suggest. The loss of cells was quite diffuse. The Betz cells contained some unilateral or occasionally more extensive deposits of pigment. The frontal and calcarine areas contain little or no nerve cell pigmentation (Heidenhain). The general neuroglia cell pigmentation was prominent, particularly in the calcarine region. Perivascular cell pigmentation slight. It is impossible to say what relation was borne by the slight cerebral atrophy to the paranoic and hallucinatory conditions of this case. The brain weighed 1340 grams and therefore belongs in the overweight series rather than in the underweight series.

Case 6, female, became eccentric about 60, developed persecutory religious delusions, at 70 showed a moderate peripheral arteriosclerosis, showed at two intervals a few katatoniform symptoms (possibly in reaction to delusory fear), developed some delusions concerning viscera, preserved memory and orientation till death at 77 from pulmonary tuberculosis. The cerebral pigmentation in this case (one of the later ones to be examined) was noted in the gross and proved to be the chief feature of the microscopic examination. Brain weight, 1130 grams. Perivascular cell pigmentation moderate throughout. Neuroglia cell pigmentation well marked and general. Practically all the nerve cells are pigmented in the frontal areas, where the layer of external pyramids shows unusually prominent deposits. The nerve cell pigmentation in the postcentral gyri (precentral not accessible) and in the calcarine area is moderate only.

Case 7, female, had inflammatory rheumatism at 55, lay in almshouse by reason of contractures, developed delusions of a persecutory character 65-

70, had auditory hallucinations, preserved orientation, memory, school knowledge, and interest in surroundings till death at 75 from bronchopneumonia and chronic diffuse nephritis. The brain showed basal cerebral arteriosclerosis, was underweight (1180 grams), and showed chronic leptomeningitis. The pigmentation of the perivascular cells was in all regions moderate, there was a moderate pigmentation of neuroglia cells in the white matter. The nerve cell pigmentation was both of the yellow saccular kind and of the diffuse brown kind, and was more marked in the motor areas. We deal in this case once more with a comparatively simple cerebral atrophy.

Case 8, male, alcoholic laborer, luetic (?) at 52, died about a month after the development of weakness, disorientation, amnesia, visual and auditory hallucinations. Ten days before death rectal temperature 91.4; within 24 hours, temperature gradually rose to 101.8. Death in stupor. Ecchymoses of stomach. Chronic diffuse nephritis. Moderate arteriosclerosis. Brain weight, 1350 grams. The nerve cells are free from diffuse pigmentation, although the Betz cells show yellow saccular pigment. The nerve cells of the frontal region are free from pigment. There is a moderate general neuroglia cell pigmentation and a moderate perivascular cell pigmentation. The interpretation of this case remains, so far as we can discover, quite obscure. An alcoholic element is possible.

Case 9, male, developed delirium and inflammatory rheumatism following otitis media at 50, at 54 gave up work, failed physically, showed arteriosclerosis, had an attack of unconsciousness lasting two hours, two weeks before admission to the hospital, in hospital showed amnesia with fabrications, auditory hallucinations, restlessness, and weakness, and died at 56 of hypostatic pneumonia and fatty heart. Arteriosclerosis was confined to the aorta. The brain weight was not recorded but was probably within normal limits. The microscopic examination showed a considerable general neuroglia cell pigmentation; but the nerve cells are as a rule free from either diffuse brownish pigment or yellow saccular pigment. The satellite cells are as a rule free from pigment. Perivascular cell pigmentation everywhere moderate.

Case 10, female, 55, had shown effects of cardiorenal disease for six months, in hospital showed disorientation, amnesia, visual and auditory hallucinations, feebleness and restlessness, and died 12 days after admission from the effects of her somatic disease. Brain weight 1300 grams. The microscopic examination showed a subpial gliosis of the frontal region, a general perivascular cell and neuroglia cell pigmentation, and in all regions examined a tendency for the cells in the external pyramidal layer to show considerable diffuse brownish pigment. The satellite cells also showed similar pigmentation. The Betz cells of the precentral gyrus were less markedly pigmented than the external pyramids.

Case 11, male, had inflammatory rheumatism in early life, gave up work 66-67, from 67 to 70 had two short delirious episodes, entered the hospital with pronounced cardiorenal signs, disoriented, amnesic for recent events, and died at 70. The brain showed focal basilar and unilateral Sylvian arteriosclerosis, with a cyst of softening external to tip of posterior cornu of right lateral ventricle. There was a dense subpial gliosis. There was a moderate and somewhat variable neuroglia cell pigmentation throughout the regions examined. The accumulation of pigment in perivascular cells is everywhere moderate. A remarkable feature of this case is the almost total absence of nerve cell pigmentation in all the areas examined.

Case 12, female, from 52 had attacks of exhilaration and depression of irregular duration, at 68 showed arteriosclerosis and malnutrition, and died at 69, maintaining memory and orientation almost to the last. There was a terminal exhaustion period of gradual onset of several months' duration. Death from hypostatic pneumonia, pleurisy, pericarditis, and mediastinitis. General arteriosclerosis was marked. Chronic diffuse nephritis. General encephalomalacia and myelomalacia (of terminal infective or toxic origin?). The brain weighed 1135 grams. There was a frontal (including orbital) and central convolutional-sclerosis. Corresponding therewith subpial gliosis was considerable. Perivascular cell pigmentation is nowhere extreme and is as a rule slight. Neuroglia cell pigmentation, practically absent in white matter and in subpial zone, is prominent in the nerve cell layers and especially in the substellate region. The neuroglia cell pigmentation is shown in its extremest form in the calcarine region. Satellite cell pigmentation is nowhere marked. The nerve cells rarely show more than a unilateral collection of small granules or a few peripheral granules. No distinction between large and small cells can be remarked with respect to this dark pigment.

Case 13, male, developed at 63 an unreasonable attitude to his family, with flight of ideas and violent tendencies, and, on transfer to insane hospitals maintained his abusive and annoying conduct, elation, and psychomotor activity for four years. Death from multiple injuries at 67. The brain showed chronic pial changes, notably along vessels, a basal cerebral arteriosclerosis of moderate degree, atrophy of the frontal cortex, and a focal area of softening of one paracentral lobule. The microscopic examination showed neuroglia cell pigmentation in the white matter and in the subpial region, but to a great degree absent from the nerve cell layers (frontal). There was a moderate degree of perivascular cell pigmentation throughout. The nerve cells were in almost all instances quite free from any type of pigment. In a few nerve cells occurred a small collection of pigment granules on one side of the cell. The distribution of the neuroglia cell pigmentation (in the subpial region and white matter) seems to indicate its origin in myelin decay. The occipital cortex, though it showed no gross atrophy, showed a slight degree of microscopically observable subpial pigmentation. The white matter of the occipital region was largely free from pigment. The precentral gyri form an exception to the general rule of pigment absent in nerve cells, since occasional large cells (Betz and external pyramids) show considerable pigmentation.

Case 14, female, became maniacal at 57 and remained so till death at 70 of generalized tuberculosis. The brain weighed 1110 grams and showed a subpial gliosis, well marked in frontal and extreme in central regions. The white matter and the subpial region showed a moderate neuroglia cell pigmentation in all regions examined. Perivascular cell pigmentation was moderate throughout. Conditions varied with respect to nerve cell pigmentation; the external pyramids of the frontal region, the Betz cells of the precentral gyri, and the solitary cells of Meynert in the calcarine region contained much diffuse brownish pigment. A remarkable feature of the frontal sections was that, although the internal pyramids showed far less pigmentation than the external pyramids, the neuroglia cells of the internal pyramidal layer were much more highly pigmented than the neuroglia cells of the external pyramid layer. Yellow pigment was also very prominent in the precentral large cells. The smaller nerve cells nowhere showed much pigmentation. The interpretation of these microscopic findings is difficult and doubtless impossible with the data at hand.

Case 15, male, became hypochondriacal at 56, later restless and suicidal, was committed, maintained memory and orientation, and developed feelings of unreality and nihilistic ideas. Death at 58 from chronic diffuse nephritis. Brain weight, 1370 grams. The microscopic examination failed to show nerve cell pigmentation, but showed a slight satellite cell pigmentation in the frontal region. Some of the large cells of the precentral gyri showed pigmentation, and there was both satellite cell and general neuroglia cell pigmentation in this region. Elsewhere a moderate general neuroglia cell pigmentation and perivascular cell pigmentation.

Case 16, female, became depressed at 65 after nursing husband, showed arteriosclerosis and albuminuria, developed increasing defect of attention and amnesia for recent events, auditory hallucinations, and feelings of unreality, agitation, and insomnia. Death from infection following accidental wounds six months after commitment. Brain weight, 1220 grams. A single patch of sclerosis was found in the right Sylvian artery. The microscopical examination showed very little perivascular cell pigmentation. The neuroglia cell pigmentation is moderate and begins to be prominent only in the layer of external pyramids. Nerve cell pigmentation, slight in frontal and calcarine areas, is more extensive in the motor area. The external pyramids of the frontal and the Betz cells show more pigment than other nerve cells, and the brownish pigment is combined with yellow pigment in these cells.

Case 17, male, had had delirium in grippe and typhoid fever at 61, became depressed, sleepless, and thin at 65, developed feelings of unreality and nihilistic delusions and died within six months of onset with cystitis, retroperitoneal suppuration, thrombosis of right auricle and of aorta, and pulmonary embolism. The microscopic findings yielded a suspicion of paralytic dementia from the occurrence of a moderate lymphocyte and plasma-cell exudate in the meninges (normal in the gross) ; but the absence of notable alterations in the nerve cell layers seems to exclude this suspicion. Perhaps the extensive suppurative process in the trunk may be related with the meningeal exudate. The large nerve cells failed to show brown pigmentation (notably the Betz cells and the solitary cells of Meynert), but the smaller nerve cells (such as those of the outer cell layers) showed well-marked brown pigmentation. The neuroglia cell pigmentation and that of the perivascular cells presented nothing characteristic, being moderate and of general distribution.

Case 18, female, developed at 58 insomnia, hallucinations, persecutory delusions and financial worry, showed peripheral arteriosclerosis, albuminuria, exaggerated reflexes, remained apprehensive, imperfectly oriented, and tardy in answering questions, and became increasingly depressed and restless, dying, two months after onset, of enteritis. There was thrombosis of a branch of the right Sylvian artery. Brain weight, 1330 grams. Microscopic examination showed slight perivascular cell pigmentation, considerable neuroglia cell pigmentation in the nerve cell layers, and extreme nerve cell pigmentation rather more characteristically in the substellate layers but sparing neither large nor small cells. (The calcarine region was not accessible in Heidenhain preparations.) Satellite cell pigmentation was variable in degree: near some cells maximal, but in general not much in evidence.

Case 19, male, alcoholic in early years, at 70 grew depressed, threatened, and finally attempted suicide. He was anemic and showed peripheral arteriosclerosis, somewhat retarded in responses, slightly amnesic, deluded concerning family, and constantly depressed. Death after gradual physical failure from acute pleurisy developing upon chronic pulmonary tuberculosis with apical abscesses. There was basal cerebral arteriosclerosis, focal atrophy of one opercular region and chronic internal hydrocephalus. Brain weight, 1240 grams. Microscopically, gliosis of the outer layer was marked. Perivascular cell pigmentation was moderate or slight. Neuroglia cell pigmentation was everywhere marked. And, although the nerve cells nowhere contain much brown pigment, the satellite cells in many places show much brown pigment. The large nerve cells of the frontal and precentral gyri contain much yellow saccular pigment.

Case 20, male, attempted suicide at 52 after financial worry, shortly improved, but grew depressed once more, developed auditory hallucinations, and was committed in a feeble, apprehensive, retarded, partially oriented state. Frightful auditory hallucinations. Self-accusations. Restless agitation. Death three months after onset, from aspiration pneumonia. There were no gross lesions in the brain. Microscopically, perivascular and neuroglia cell pigmentation were slight or moderate throughout. The subpial region of the frontal gyri contains neuroglia cells enclosing very large pigment granules. Nerve cell pigmentation moderate, though some of the large cells of the calcarine region have considerable brown pigment. There are small local accumulations of brown pigment granules in some cells. The large nerve cells of the precentral gyri contain little pigment.

Case 21, male, after two years financial trouble, grew depressed and self-accusatory and expressed fear of injuring family or himself, on admission six months later, showed tuberculosis of lungs, unequal knee jerks, depression, slow motions, auditory hallucinations. Memory and orientation were maintained until death at 54, from bilateral advanced pulmonary tuberculosis. Brain weight, 1410 grams. One olfactory tract absent. Microscopically, considerable perivascular and general neuroglia cell pigmentation. The nerve cells, especially those of the external pyramidal layer, were loaded with brown pigment.

Case 22, female, developed at 55 restlessness, self-depreciation, suicidal ideas, showed arteriosclerosis and albuminuria, on commitment, and then developed a depressed inactive state with distressing visual hallucinations at night, became retarded, but preserved orientation and fairly good memory until death at 59. Acute purulent pericarditis. Atrophy of liver (simple), 760 grams. Renal atrophy. Brain weight 1040 grams. Microscopically, perivascular cell pigmentation slight, neuroglia cell pigmentation slight except in the frontal subpial region where it is moderate and in the calcarine region where it is marked. The nerve cells are characteristically free from pigment. The Betz cells are likely to show a few pigment granules round the periphery and occasionally show extreme pigmentation.

Case 23, male, alcoholic in early years, 10 years temperate, became depressed and attempted suicide at 64, recovered in a few months, worked at the hospital as machinist and died at 72 of tuberculous peritonitis. The brain showed slight chronic fibrous leptomeningitis weight 1310 grams. Microscopically, there was slight perivascular cell pigmentation. The neuroglia cell pigmentation is general and intense. The nerve cells tend to show granules in all parts of the cell body. The larger cells tend to show relatively less pigment.

VI. (a) Correlations with Arteriosclerosis.

Arteriosclerosis was clinically recognizable in 10 cases and was found anatomically in 20 cases. There was marked general arteriosclerosis in four cases, aortic sclerosis in 18, sclerosis elsewhere than in the aorta in 12. Nine cases showed cerebral arteriosclerosis.

Heart disease was clinically recognized in nine cases, anatomically in 12 cases.

Kidney disease was clinically recognized in nine cases, anatomically in some degree in 21 cases, but markedly in 11 cases.

The cases of marked general arteriosclerosis are not those which show cardiac hypertrophy (except in Case 3), whereas three of the marked arteriosclerotics (not including Case 3) show well-marked kidney lesions.

It does not appear from a review of the histories in the four well-marked arteriosclerotics that arteriosclerosis had necessarily anything to do with the insanities. The durations of insanity in these cases were 10-12, 22, 17, and 17 years, respectively, and their ages at death were 68, 72, 77, and 69, respectively. These cases have with one exception (Case 14, 13 years) the longest durations in the series.

The onset was gradual in 16 cases, sudden in seven cases.

There were but seven cases with peripheral motor or sensory disorder; these disorders were largely trivial in character. Knee jerks were absent in one case, unequal in two.

Evidences of focal brain lesion were clinically found in four cases, one 8-10 years after onset, one a doubtful "shock" two months before death, one a single convulsive seizure six years before death, one a period of two hours' unconsciousness 23 days before death.

Anatomically, only one of these four showed focal lesions (Case 3), but four others (Cases 4, 11, 13, 18) showed focal lesions unsuspected during life.

Of the four well-marked arteriosclerotic cases, three were paranoic and one maniacal. Of the five cases with cysts of softening in various regions, two were paranoic, and one each delirious, maniacal, and depressive cases.

There seems to be no good ground for asserting that arteriosclerosis runs parallel with these insanities or has much more than a complicating relation to them. It remains, of course, possible that arteriosclerosis may, sometimes and under certain conditions, bring about the structural and functional necessities for the development of insanity; but this point will be exceedingly difficult to prove.

(B) CORRELATIONS WITH SENILE ATROPHY.

Do these cases stand in a closer relation to senile atrophic processes than to the arteriosclerotic processes just considered?

The weights of 18 brains in this series are recorded; and atrophic processes in the others can be decided safely from notes or microscopic description. Seven (probably eight) of the female brains weighed less than 1235 grams, three weighed over 1235 grams, five (probably six) of the male brains weighed less than 1358 grams, three weighed over 1358 and three were not recorded but probably weighed within normal limits.

The seven (probably eight) underweight female brains all weighed less than the lightest male brain. The lightest brain (Case 22, 1040 grams, representing a diminution of about 15 per cent from the average weight) occurred in a case with liver weighing but 760 grams and with very small kidneys. The duration of mental disease in this case was four years. The durations in the remaining underweight female brains were (four, 1110 grams, 22 years; 14, 1110 grams, 13 years; six, 1130 grams, 17 years; 12, 1135 grams, 17 years; seven, 1180 grams, 5-10 years; 16, 1220 grams, six months; five regarded as atrophic, six years). Such durations indicate the possibility that the atrophy supervened upon the mental disease in several instances; but the conditions in Case 22 seem remarkable. In the female cases with overweight brains, the data are: 10, 1300 grams, five months, æt. 55; 18, 1330 grams, two months, æt. 58; three, 1365 grams, 10-12 years, æt. 68.

In the case of the male brains, the deviations are not so great, and the durations are far briefer (19, 1240 grams, one year; one, 1250 grams, six years; 13, 1310 grams, four years; 23, 1310 grams, mentally capable at death; eight, 1350 grams, brief; 15, 1370 grams, two years; 21, 1410 grams, three years; two, 1430 grams, two years; nine, probably normal weight, six years; 17, probably normal weight, six months; 20, probably normal weight, three months).

It therefore appears that, though there is much more atrophy in these female brains than in the male, the duration of life beyond the onset of mental disease is also far greater in these females. It is therefore, natural to suppose that the atrophy is here a function of longevity rather than one of mental disease.

(c) Distribution of Cortical Pigments.

Inclined to the conviction that both arteriosclerosis and atrophy are merely complicating features in the insanity of these subsenile decades and that we must look elsewhere for the causes and structural conditions of the insanities here discussed, we examined the tissues with a view to obtaining further light from the microscopic side. Aside from the apparently non-essential degenerations and tissue losses incidental to arteriosclerosis and atrophy, are there any essential alterations, either destructive or non-destructive, involving cells or fibers or the investing neuroglia in these conditions?

We had previously described three cases (one of which, Case 17, is reproduced in this paper) of depression in which the factors of arteriosclerosis and simple atrophy could reasonably be excluded from a causative rôle. In these cases our attention had been especially levelled at certain intracellular pigmented substances. These substances, demonstrable in several ways, were particularly well brought out in Heidenhain iron-hematoxylin preparations after alcohol fixation.

The interesting feature of the former study was that these pigmented substances were accumulated largely in the bodies of the smaller nerve cells in various cortical regions, perhaps more particularly in the suprastellate nerve cell layers. The large cells, such as the Betz cells of the precentral gyrus and the solitary cells of Meynert in the calcarine region, were free from these substances.

The confinement of these deposits to the smaller cells and their absence from the large (projection) cells suggested an attractive line of attack on the histology of the cortex in mental and other disease. We have, therefore, paid especial attention to these intracellular deposits in the present series of cases. The deposits of pigmented substances which can be brought out by the Heidenhain iron-hematoxylin method are found in (1) cells of a phagocytic character lying in the adventitiæ of vessels, (2) neuroglia cells, (3) nerve cells.

Our results in this field are so far wholly qualitative and are based upon estimates of the iron-hematoxylin staining substances in comparatively few areas from each case, as a rule frontal, precentral, calcarine. So far as our results go, however, they are of some interest.

Perivascular cell pigmentation was a constant feature in all 23 cases. We interpret this to mean merely that certain products of tissue metabolism are not being discharged completely from the tissues. And it is our general experience, in accord with that of others, that pigmented material is perhaps constantly found in the perivascular regions of the brains of persons of middle age. It is not an infrequent feature in brains of persons, regarded as normal, in the fifth decade. It is a remarkable feature of our results at this stage that the perivascular cell pigmentation is of fairly even degree in all the areas examined from any one case and that, consequently, the perivascular deposits do not afford an index of the varying metabolism of different areas of the cortex. It is possible, however, that investigation of further cases will reverse this conclusion.

Not every case in our series showed the same degree of perivascular cell pigmentation. Both the male case with lightest brain (19) and the female case with lightest brain (22) showed slight perivascular deposits. The tissues showing least perivascular deposits were from Case 16, female, æt. 65, an agitated sleepless melancholic, with brain weight 1220 grams.

There are more significant variations in the *neuroglia cell pigmentation,* which like the perivascular deposit was shown in every case. Whereas the perivascular deposits seemed to occur in similar amounts in all areas of a given cortex, the neuroglia cell deposits in several cases varied in degree from area to area: in particular, three cases (1, 5, 22) showed more extensive deposits in the calcarine and occipital neuroglia cells, and Case 1 also showed extensive deposits in the precentral area. The significance of such variations is not apparent.

Intragyral variations in the degree of neuroglia cell pigmentation were noted in seven cases. In only one of these (Case 11) were the variations of an irregular and apparently capricious character. In Case 13 the frontal cortex showed little or no neuroglia cell pigmentation in the nerve cell layers, but considerable in the subpial zone and in the white matter: this may probably show that the neuroglia cell pigmentation is an index of myelin decay in some instances. Opposite conditions held in Cases 12 and 18, where the neuroglia cell pigmentation was more or less sharply confined to the nerve cell layers. Still more differential conditions were found in Case 14, where the neuroglia cells of the layer of internal pyramids were more highly pigmented than those of the layer of large external pyramids, and in Case 16, where the neuroglia cell pigmentation began to be marked only in the layer of large external pyramids and in lower layers.

The most marked neuroglia cell pigmentation occurred in Cases 19 (a depressed case, æt. 70, formerly alcoholic) and 23 (a depressed case formerly alcoholic, for seven to eight years without active mental disease, dead at 72). The least extensive deposits in neuroglia cells occurred in Case 20 (a depressed case, not alcoholic, dead at 52, after three months' symptoms). The factors of age and alcoholism may possibly therefore influence these deposits in the bodies of the neuroglia cells.

More striking variations are shown by the amounts and distribution of iron-hematoxylin-staining *pigment in the nerve cells*. Although it is probable that no brain was absolutely free from traces of such pigmentation, yet four cases (eight æt. 55, nine æt. 56, 11 æt. 70, 19 æt. 71) showed extremely little pigment in the nerve cells. Of these, eight showed the "senile" yellow pigment in the Betz cells and 19 showed yellow pigment in the larger nerve cells of both frontal and precentral gyri. Case 19 was also remarkable in that the satellite cells were often highly pigmented whereas their adjacent nerve cells were pigment-free. The almost total absence of pigment in 11 is surprising in the presence of focal arteriosclerotic lesions and atrophy.

Cases 5 æt. 72, 12 æt. 69, 13 æt. 67, 15 æt. 58, 22 æt. 59, form a group in which a slight but noteworthy amount of nerve cell pigmentation occurred. In 13, 15, and 22, the precentral area showed considerable pigment whereas other areas were comparatively free. It is a curious coincidence that all three of these cases showed conduct disorder (13 destructive and violent, 15 and 22 suicidal).

More marked pigmentation with some stratigraphic variation is shown by a group of 11 cases (1, 2, 6, 7, 10, 14, 16, 17, 18, 20, 23). The suprastellate layer of pyramids seems to be marked for special pigmentation (Cases 2, six (frontal), 10, 14 (frontal), 16 (frontal)). Of these cases, five (2, 6, 10, 17, 23) belong in the class (described in our former paper on melancholia), of cases in which the large (projection) cells are relatively pigment-free, whereas the smaller cells are pigmented. Cases 20 and 22 show the opposite relations. Case 1 showed pigment in the Betz cells but the homologous solitary cells of Meynert were pigment-free.

VII. Conclusions.

Arteriosclerosis and *senility,* separately or combined, have been very handy terms in psychiatrical diagnosis. However, we believe we have proved conclusively, by the present analysis, that neither old age changes nor arterial disease have any necessary connection with the development of insanity in the later years of life, at least in the sixth and seventh decades. It seems probable that *arteriosclerosis, senility,* and various forms of *insanity* are entities which frequently interpenetrate, but are logically and genetically quite separate. Even the degree to which old age and arterial disease serve as *complicating factors* in insanity has been much overestimated.

The constructive part of our paper looks in the direction of the distribution of intracellular pigments, a species of work harking back to the somewhat neglected field of Bevan Lewis (1890). The perivascular cell pigments, according to our comparisons, seem to afford some index of the degree of faulty metabolism of the cerebral tissue: these pigments are deposited in like amounts throughout a given brain. The neuroglia cell pigments, in the light of the present material, vary rather with the age of the individual. The nerve cell accumulations are subject to the greatest variations even in a single brain, certainly do not vary with the age of the individual, and vary according to some undetermined principle.

We have omitted literary references in the present paper, but wish to express our gratitude to Prof. A. M. Barrett for the use of some of his Danvers Hospital material. Our work may be regarded as in some sense a complement to Barrett's Study of Mental Diseases Associated with Cerebral Arteriosclerosis (*Am. Jour. Insanity,* LXXII, 1, 1905). Our cases are from the same general source as Barrett's cases, but are in no instance identical therewith.

It would be of some value to fuse with the present analysis a similar analysis of the frankly organic cases of the same epoch, in order to pick out, if possible, the special constituents of the mental picture produced by the gross lesions. This task we have in hand.

Our results briefly are:

1. Twenty-three cases of insanity, presumed to arise in the sixth and seventh decades, have been studied clinically and anatomically. Two of these were alcoholic in origin. Five were paranoic. Four were cases of delirium. Three were maniacal. Nine were cases of depression.

2. Two of the paranoic cases developed katatoniform symptoms and might be placed in the dementia præcox group.

Seven cases are possibly classifiable in the manic-depressive group. Two of these had attacks of retardation. One case remained maniacal for 13 years. One case recovered from a single suicidal depression and died eight years later of intercurrent disease.

3. Neither general nor cerebral arteriosclerosis bears an essential causative relation to the insanities developed in the sixth and seventh decades by the 23 cases clinically and anatomically studied.

4. The insanities arising in these decades are not characteristically due to the premature onset of senile atrophy. Eight out of 11 female brains were atrophic: the average age at death was 69.8; the average duration 10.8 years. Five out of 12 male brains were atrophic: the average age at death was 65.6; the average duration 2.7 years.

Either the female cases are more liable to brain atrophy and to live longer with atrophied brains or else the atrophy is merely a function of their greater age at death. The average age at death in all 11 females is 67.2; the average duration 8.8. The average age at death in all 12 males is 62.3; the average duration 2.8. The differences in age at onset: female average 58.4 (atrophics, 59.8), male average 59.5 (atrophics, 62.9), are not great.

5. A comparative study of the distribution and extent in several cortical areas of certain pigmented materials demonstrable by iron-hematoxylin (among other methods) brings out extreme and interesting variations in the cases examined.

Perivascular cell pigmentation is almost uniform in different areas of the same case, bar focal destructive lesions, but varies in degree in different cases.

Neuroglia cell pigmentation, when of general distribution, probably varies more or less directly with age.

Nerve cell pigmentation (iron-hematoxylin) is not a function of age. It is premature to relate the amounts and distributions of nerve cell pigments with different mental diseases.

TYPHOID MENINGITIS: CULTIVATION OF BACILLUS TYPHOSUS FROM MENINGES AND MESENTERIC LYMPH NODE IN A CASE OF GENERAL PARESIS, WITH NOTE ON EXPERIMENTAL TYPHOID MENINGITIS IN THE GUINEA-PIG

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I. We have to report a case of typhoid meningitis. The case presents certain unusual features. The bacillus typhosus was obtained in pure culture from the meninges and from a mesenteric lymph node, but was not present in the heart's blood at autopsy. There was no anatomical sign of typhoid fever except mesenteric lymph node swelling. The absence of typhoid lesions from the intestinal wall was especially noted by reason of the peculiar isolated lymph node swelling and was striking because the intestinal wall was actually thinner than normal. Such thinning of the intestinal wall is a not infrequent feature in advanced general paresis of the insane, of which the patient was a victim.

It appears that typhoid meningitis has occurred almost uniformly as an incident in typhoid fever of intestinal type. Every case of true suppurative typhoid meningitis with autopsy, as tabulated by Cole,[1] of Baltimore, has proved to be coincident with intestinal lesions. Cole has gathered twelve such cases from the literature and has added a thirteenth case from the Johns Hopkins clinic. Wentworth's case of a child of four years, from whose meninges the

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* Read at the Ann Arbor meeting of the American Association of Pathologists and Bacteriologists, May, 1908. The paper represents a part of the work done under a grant from the Proctor Fund (1907-8). Received for publication Oct. 13 1908.

bacillus typhosus was cultivated by lumbar puncture, died, but unfortunately was not autopsied.[2]

The present case might have given rise to the suspicion of a primary typhoid meningitis, had it not been for the positive mesenteric lymph node culture. We were led to the latter finding partly through noting the condition of the nodes at autopsy and partly through our study (not yet published) of infection with Bacillus coli communis along the same path. The present finding came as a surprise in a set of routine cultures from cerebro-spinal fluids and lymph nodes.

Not only was there no sign of typhoid fever at autopsy, but also during life the terminal symptoms were inextricably massed with phenomena of general paresis. The patient had for years been under medical care and no symptoms even remotely resembling those of typhoid fever had ever been noted. There were no gall stones. Unfortunately no Widal reaction was performed with the patient's blood either before or after death. The isolated organism was clumped by anti-typhoid rabbit serum 1–50,000.

II. Clinical history. — The details of the present case follow: A salesman of thirty-one was admitted to the Danvers Insane Hospital June 2, 1906, and died there Nov. 29, 1907. The patient contracted syphilis at nineteen. He married at twenty-two and had two children, still living. There were no miscarriages. Difficulty with bowels and bladder followed marriage. Patient was treated for bladder disease by Dr. Abner Post. At twenty-eight patient lost control of limbs and was confined to the house about two months, under the care of Dr. L. R. G. Crandon. Three months later he had regained partial control of his limbs, but had lost all control of his sphincters. After another month he had returned to work, but did not work steadily and seemed to have lost ambition. In the summer of 1905, his mind became obviously altered. He grew indolent and extravagant and given to buying expensive and useless articles. Loss of interest in things followed, together with loss of memory for recent events, lack of insight into illness, delusions of persecution by wife, irascibility followed quickly by crying. Before admission to hospital, he was euphoric, drawling and tremulous in speech, sprawling in penmanship, alternately depressed and exalted in manner. Knee-jerks were absent, gait ataxic, pupils stiff to light.

The family history was negative with respect to insanity. All the family are reported as nervous. A brother died of peritonitis at twenty-eight, a sister of pneumonia under twenty. Another brother and sister are living. Father and mother died of heart trouble at about sixty-seven and sixty respectively.

The patient was at high school one year and was a fair student. Considerable tobacco was used, and some alcohol. Intoxication denied. There was no history of typhoid fever or other acute disease.

The patient on admission was sallow, poorly nourished, and flat-chested, with a slight lateral curvature. There was slight dulness over right apex in front and in right upper back. Voice sounds were increased over right apex in front and over whole right back. The right chest showed bronchial respiration throughout. The respiration in front of right chest was of an interrupted character. The liver seemed moderately enlarged. The urine showed a very faint trace of albumin. There were a few small nodes in right groin and a scar on dorsum of penis.

NEUROLOGICAL EXAMINATION. — Slight swaying in Romberg position. Slight tremor of protruded tongue and extended fingers. Pupils irregular, left slightly larger than right. Left pupil reacted to light consensually, but not directly. Right pupil reacted very slightly to direct light, not consensually. Knee-jerks and Achilles jerks absent. Ankle clonus absent. Abdominal and cremasteric reflexes brisk. Sharp and dull points were recognized in the legs with numerous mistakes.

Vocal and facial tremor. Speech slow and drawling. Test phrases repeated well if care was taken. Consciousness clear. Orientation perfect. Calculating ability preserved. Many words omitted in writing. Penmanship clear but shaky. Hallucinations absent. Memory of recent events poor. Associations of a logical or defining type.

Patient denied various statements in commitment papers and had little or no insight into the mental side of his disease — slight euphoria.

After a month's observation the patient was removed to a quiet ward and set to work a few days in the scullery. One night he began to yell as if assaulted and said later that he had an idea that he was going to die. Before three months had passed he had become untidy, disorderly, and imperfectly oriented.

The general degeneration continued rapidly. One week before death the temperature rose to 103° F. and the patient succumbed to what seemed clinically like a bronchopneumonia. Unconsciousness two days before death.

Note with respect to history of typhoid. — Inquiries of his physicians, wife, employer, and brother tend to show conclusively that the patient never had a disease even remotely resembling typhoid fever.

CLINICAL SUMMARY. — Male without history of typhoid fever. Syphilis at nineteen. Marriage at twenty-two (two healthy children, no miscarriages). Disturbance of bladder and rectum. Successful in business (salesman) till twenty-eight, when advancing tabes confined him to bed for a time. At thirty mental signs of general paresis developed. Death at thirty-two after an acute illness of a week.

III.

The autopsy was performed sixty-seven hours after death by Drs. E. E. Southard and M. M. Canavan. Following is a copy of the protocol:

Well developed, emaciated white male; one hundred and sixty-five centimeters long. Lividity of dependent parts. Rigidity of limbs and neck. Pupils: left, 2.5 millimeters; right, four millimeters. Abdominal fat, one centimeter deep. Decubitus absent. Penis and scrotum show reddish discoloration.

Peritoneal cavity. — Walls not remarkable. Omentum thinly clad with fat. Mesenteric lymph nodes slightly enlarged, one measuring 2.5 x 1.5 x .5 centimeter. Diaphragm arches to fifth space on both sides.

Pleural cavities. — Both free from adhesions. Visceral surface of the *right* lower lobe shows delicate early fibrin, in small readily detachable strips. Pleural cavities contain a slight amount of fluid.

Pericardial cavity. — Slight excess of fluid. Pulmonary vessels give no evidence of ante-mortem clot.

Heart. — Weight, two hundred and ninety-five grams. Epicardial fat moderate in amount. Muscle firm and red, without evidence of increase of interstitial tissue. Endocardium of auricles and of right ventricle normal. Endocardium of left ventricle mantled with a thin layer of connective tissue, especially well marked towards the aortic valve. Valves normal, except mitral, which shows a few spots of yellowish softening both upon the edge and at various points in the curtain. Chordæ tendineæ normal. Chambers contain cruor clot. Coronary arteries show very faint, small areas of yellowish thickening, the most marked of which lies about two centimeters from the origin of the descending coronary.

Measurements: T. V., 11.5; P. V., 6.5; M. V., 7.5.
A. V., 7.5; L. V., 1.3; R. V., .4.

Lungs. — Weight, eight hundred and ninety grams, left; seven hundred and eighty grams, right. Edematous, congested, dark and semisolid behind. The posterior portions of both lower lobes show areas in the midst of the congestion which are of a grayish pink color, and leave a granular surface on section. These measure from .5 centimeter to three centimeters in diameter. Pieces from the posterior portion of the lower lobe sink in water. A moderately foul odor from the cut surface of the lower lobe. Bronchi reddened and velvety. Vessels not remarkable. Bronchial lymph nodes small.

Spleen. — Weight, one hundred and eighty grams. Border shows numerous indentations. Capsule of the usual thickness. Substance not pulpy. Substance shows innumerable small oozing hemorrhages. Malpighian bodies somewhat larger than normal. Trabeculation not remarkable.

Gastrointestinal tract. — Esophagus not remarkable. Stomach small; walls thin and without rugæ. The remainder of the tract shows walls which are possibly somewhat thinner than normal, but show no other evidence of lesion. No lesion to correspond to the enlarged mesenteric lymph node was found.

Liver. — Weight, one thousand five hundred and eighty-five grams. Border sharp. Substance of the usual firmness, or a trifle increased. Lobulation distinct. Color grayish brown. Gall bladder normal.

Pancreas. — Of a pinkish color; gives no evidence of lesion.

Adrenals. — Show softened interiors.

Kidneys. — Weight, three hundred and fifteen grams. Capsule of the usual thickness, strips with considerable ease from a reddish gray surface. Cortex of normal thickness, shows in places slight grayish opacity, suggesting fat. Pelves contain a slight amount of slightly turbid fluid, but the mucosa shows no evidence of acute inflammation. Ureters normal.

Bladder contracted, with thickened walls. Ureteral orifices patent. Prostate not enlarged. Posterior portion of the right lobe contains a pea-sized abscess cavity from which wells up yellowish gray pus. The aortic arch shows a slight degree of sclerosis with faintly puckered lines radiating from a point opposite the coronary orifice. This lesion extends about six centimeters. The rest of the aorta is normal.

Head. — Skin exceedingly loose, and the whole skull cap thinned. The diploœ are absent. Adhesion with dura easily separated. The dura somewhat thickened, but not distended. Along the longitudinal sinus extensive calcareous granulations adhere to it. The longitudinal sinus does not contain blood, and the inner surface is normal in color. The pia is extensively thickened and opaque and a general subpial exudate exists which is more marked over the vertex where it lifts the pia from the brain surface to the extent of three centimeters in Rolandic, superior frontal, intraparietal, and mesial precentral sulci on each side. The arteries at base are free from atheroma. The temporal lobes are much bound down by adhesions, as is the cerebellum. Post-mortem softening is evident. The hemispheres show no asymmetry, but the frontal convolutions are markedly atrophic. The corpus callosum is united to the cortex by old adhesions and has to be dissected away from it. Lateral ventricles contain some slight amount of cloudy fluid, and the pia among vessels is opaque. Some granulations in ependyma. Brain weight, one thousand three hundred and five grams. Pons and cerebellum, one hundred and ninety-five grams.

Cord. — Dura much thickened, and the pia corresponds to its appearance in brain with a like exudate. Cross-section of cord shows sclerosis of posterior columns.

ANATOMICAL SUMMARY.

Acute conditions:

Hypostatic pneumonia, with early serofibrinous pleuritis and without lymph node swelling; enlargement of mesenteric lymph nodes; acute cerebrospinal leptomeningitis; multiple small hemorrhages of spleen.

Other findings:

Scar of penis; sclerosis of aortic arch (Heller's type?) and slight coronary arteriosclerosis; calvarium thin and dense; dura mater thickened and adherent to calvarium; calcified arachnoidal villi; chronic cerebral and cerebellar leptomeningitis; atrophy of frontal lobes; granular ependymitis; sclerosis of posterior columns of spinal cord; emaciation; unequal pupils; slight parietal fibrous endocarditis, slight mitral sclerosis; gastrointestinal atrophy; chronic cystitis; chronic abscess of prostate.

This picture seems to accord in most of its details (1) with the sequelæ of syphilis, (2) with the characteristic findings in general paresis of the insane, and (3) with a terminal acute condition.

IV. BACTERIOLOGY. — Cultures upon agar plates were made from the heart's blood, from the largest of the swollen lymph nodes, and from the pus of the subpial region of the vertex.

The heart's blood culture yielded a single colony, which proved to be Staphylococcus pyogenes albus. No further work was done with this organism, which is possibly related with the rich staphylococcal flora of the lung of this case.

The mesenteric lymph node and cerebrospinal fluid cultures both yielded many colonies of an organism which proved to be Bacillus typhosus.

The organisms identified as Bacillus typhosus are motile, Gram-negative bacilli, usually slender, though of variable size and length. They grow upon agar as moist white (bluish white, grayish white, occasionally slightly yellowish white) translucent (occasionally opaque) colonies, varying from pin-point to one millimeter in diameter. The organisms fail to produce gas on glucose agar, produce no indol, and do not liquefy gelatine. Milk is not coagulated, but becomes slightly acid. The acidity diminishes after five days. Growth on potato colorless.

Parallel cultures upon the same batch of media were carried out with known cultures of Bacillus typhosus, Bacillus coli communis, and Bacillus paratyphosus α and β, given us by Prof. H. C. Ernst. The organism of this case paralleled in all respects the known culture of Bacillus typhosus.

The serum of a rabbit immunized against Bacillus typhosus by Dr. F. P. Gay clumped our organism in dilutions as high as one to fifty thousand.

V. MICROSCOPIC FINDINGS. — The microscopic examination of the tissues added a few features to the anatomical diagnoses:

Slight pigmentation of heart fibers; pneumonia, staphylococcal, with bronchial plugs of bacteria; slight chronic splenitis; focal necroses of liver; slight chronic interstitial nephritis; slight cloudy swelling of kidney.

Following is the result of microscopic examination of tissues in trunk:

The heart showed, in a section through the wall of the left ventricle, a trivial degree of perinuclear pigmentation affecting occasional fibers only. Pigmented fibers are more frequent in the internal layers of muscle, adjacent to the thickened endocardium. The endocardial thickening is almost purely fibrous and mononuclear cells are conspicuously absent. No lesions like those figured by Mallory[3] (Plate LVII., Fig 18) were found, or any lesions pointing to the effect of typhoid toxines.

Sections from lower lobe of lung show a very rich flora of mixed character, dominantly coccal. Many alveoli appear to have served as culture tubes for the richest possible growths of cocci, often in chains. The bronchi are sometimes completely plugged with masses and sheets of organisms suggesting staphylococci. In the bronchi and in the middle of some alveoli the masses are possibly the effect of multiplication post-mortem. Phagocytosis for these bacteria by polynuclear leucocytes is rarely seen. A few bacillary forms were seen, but there is no evidence that they are typhoid bacilli. The question of phagocytic cells, the effect of specifically typhoid multiplication, as raised by Mallory in discussing a case of typhoid fever complicated by fibrinous pneumonia,[4] is not brought up in the present case. The phagocytic cells present are pigment laden. A few instances of cells phagocytic for red blood corpuscles were seen. There are a number of instances of small hemorrhages into the alveoli, and about these accumulations of blood corpuscles the growth of bacterial masses is especially rich. Fibrin is not a prominent element in the diffuse cellular and serous exudation, but may be found in a few places. There seems no reason for regarding this pneumonia as anything but a recent hypostatic pneumonia with very prominent bacterial picture, and certainly no reason for regarding it as of typhoidal origin.

The framework of the spleen, particularly in a zone beneath the capsule, consists of trabeculæ which are set unusually close, and the reticulum of the pulp in this region is prominent. The pulp spaces contain a moderate number of phagocytic cells, which contain as a rule blood corpuscles. The spaces are as a rule not unduly dilated. Lymphoid and plasma cells are moderately numerous, but polynuclear leucocytes are occasional only. Giant cells of bone marrow type are rare findings. Fairly numerous ill-preserved mitotic figures occur in some parts of the pulp, perhaps in the plasma cells. The lymph nodules show no marked change. Small hemorrhages are prominent and frequent in the pulp. There are no organisms in association with these hemorrhages.

The liver shows a few focal necroses of the type described by Mallory[5] as characteristic of typhoid fever and ascribed by him to occlusion of liver capillaries by phagocytic cells derived chiefly from the spleen and intestine by embolism through the portal circulation. These necroses are in this liver infrequent. They occur in various parts of the liver lobule. The portal canals show in a few places evidence of accumulation of phagocytic cells, but neither these nor lymphoid and plasma cells can be considered as prominent features of the liver in this case. The fat content of the liver is low. There is small evidence of liver cell pigmentation.

The kidney fails to show the characteristic occlusion of veins in the pyramids with phagocytic cells, as described by Mallory in typhoid fever.[6] There are a few ill-marked foci of interstitial overgrowth in some parts of the renal cortex. Acute changes are represented only by a trivial degree of cloudy swelling and by destructive changes in a few isolated tubule systems (granular disintegration with tendency to formation of hyaline droplets). Some of the cells lining tubules of the pyramids contain collections of brown pigment granules.

The adrenal gland shows marked central and focal injection, a few foci of mononuclear cells in interstitial tissue, and post-mortem changes.

Prostate. — The walls of the abscess show great numbers of plasma cells. The interior shows numbers of very large phagocytic cells, containing chiefly fat. Some of the cells contain pigment. Polynuclear leucocytes are demonstrable only in relation to dead cells of some parts quite broken down. In certain places the destruction seems to have centered upon ducts and to be spreading outward therefrom; but in other places groups of plasma cells are found surrounding intact ducts. Corpora amylacea are abundant. Some intact bodies are found free in the interior of the abscess. No bacteria were demonstrated in the abscess.

Bladder. — No bacilli were demonstrable on the mucosa.

THE NERVOUS SYSTEM. — Tissues from many parts of the cerebrum and cerebellum, from the spinal cord, and from ganglia and nerves were examined by general methods and by the Weigert and Marchi methods.

The examination confirmed the clinical diagnosis of general paresis and of tabes, since there was not only an extensive chronic encephalitis, with the usual lymphocytic and plasma-cell exudate and irregular gliosis, but also a well-marked posterior column sclerosis, not unusual save in its extreme degree.

It might be surmised that some difficulty would arise in distinguishing the effects of paretic meningoencephalitis from those of the more recent typhoidal process. The well-known tendency of typhoidal processes to escape polynuclear exudation, at least until frank necrosis has set in, gave rise to the idea that the two mononuclear pictures — that of general paresis and that of typhoidal processes — might be confusing.

The picture presented by the meninges was scarcely what might be expected. Although numerous mononuclear phagocytic cells are everywhere found, yet the predominant picture is that of a polynuclear exudation.

The polynuclear leucocytes occur in greatest numbers in the tissue spaces, especially in the meshes of the lumbar arachnoid and in the spaces of the frontal and paracentral pia mater. In the lumbar region of the spinal arachnoid wide fields occur in which the cells are almost one hundred per cent polynuclear leucocytes. In places phagocytic cells occur, and in a few fields, even in the open tissue spaces, the number of phagocytic cells may rise to fifty per cent. Edema is a considerable feature in the meninges. Fibrin is found chiefly in the cerebral meninges and appears in numerous delicate strands in the tissue spaces.

One function of both large mononuclear and polynuclear cells seems to be phagocytosis for fatty materials. This can be well demonstrated by the Marchi impregnations, which show both types of cell to be fat-containing.

VI. Mallory suggested in 1898 that "careful bacteriological and histological study of the various complications of typhoid fever, and especially of cases of meningitis claimed to be due to the typhoid bacillus alone, may throw additional light on the character of the lesions produced by the typhoid bacillus."[7]

Mallory's histological evidence indicates that the essential lesion of typhoid fever is a proliferation of endothelial cells. The proliferation is diffuse but more marked in the lymphoid tissue of the intestine and mesenteric lymph nodes. The histological evidence points to the production by the typhoid bacillus of a soluble toxine. Mallory believes that this toxine is produced within the lumen of the intestine and diffuses along the lines of absorption through the lymphatics and along the lines of distribution through the circulation. Strictly speaking, therefore, the presence of the typhoid bacillus is not necessary within the tissues of the body for the production of the essentially typhoid lesions. The toxine alone could set up processes which, so far as we can see, might terminate in the same miliary necroses, due to endothelial-cell infarctions, that characterize typhoid fever as it occurs.

How then are to be explained cases of abscess, pneumonia, and meningitis, reported as due to Bacillus typhosus? Has the typhoid bacillus under some circumstances a truly pyogenic character? Mallory's material permitted the study of spleen abscesses and pneumonic lung in which the typhoid bacillus was present.[8] Study of the tissues inclined to the belief that the typhoid bacilli in the spleen abscesses had merely found there a favorable medium for growth and that the main effect of the bacilli in the pneumonic lung had been to complicate a lobar pneumonia with the proliferation of cells in the alveolar walls. The general conclusion is, therefore, that the typhoid bacillus has not been proved to be a pus-producing organism. The focal and purulent lesions of typhoid fever are either instances of infected infarcts due to typhoid toxine and subsequently invaded or occupied by bacteria (often by the typhoid bacillus itself) or else instances of focal lesions due to other causes than typhoid toxine and subsequently invaded or occupied by bacteria.

The position of typhoid meningitis is therefore almost crucial in this issue. With so simple a tissue as the meninges, as MacCallum[9] has again emphasized, the nature of the pure effects of the typhoid bacilli or their toxines should be made clearer. MacCallum has studied a case of typhoid meningitis coming to autopsy in the Johns Hopkins clinic. His conclusions follow the general trend of Mallory's argument. MacCallum finds nothing peculiar in the histological study of typhoid meningitis, unless it be the relative abundance of large phagocytic cells, found particularly about the veins, but also scattered through the tissues.

Although not studied in the light of Mallory's data, the cases of Ohlmacher[10] must be reviewed in this connection. Ohlmacher had reported in 1897 two cases of typhoid meningitis from the Cleveland City Hospital.

Ohlmacher's cases both died in the fourth week of recognized typhoid fever and both showed the usual intestinal lesions. The first case was delirious in the last week of life and several times passed urine involuntarily. In the second case there were no symptoms by which the date of meningitis could be fixed; the patient was either delirious or comatose throughout the thirteen days of his hospital stay. The descriptions of exudate found indicate the predominance in the first case and in parts of the second case of proliferated endothelial cells and mononuclear leucocytes. But one block from the first case was examined. Two blocks from the second case showed abundant and closely packed polynuclear leucocytes with fragmenting nuclei together with endothelial cells; a third block showed a predominance of endothelial and mononuclear cells, resembling the appearances of the first case.

The second of Ohlmacher's cases seems to have been severer than the first, since it showed an acute endarteritis. There are no notes in the cases indicating phagocytosis of the bacilli, which were abundant in the fibrinous and cellular exudate and in the lymph spaces of the first case and existed in countless myriads in dense lines in the meningeal lymphatics or scattered among the cells of the second case. It is noteworthy that the two regions of the second case which showed polynuclear leucocytosis were the regions which showed endarteritis.

It will be worth while to summarize MacCallum's findings, since his appears to be the first thoroughly examined case since Ohlmacher's.

Microscopic examination in MacCallum's case showed histological appearances identical throughout the cerebral, basal, cerebellar, and spinal meninges, varying only in intensity. Fibrin was considerably developed, but the picture is largely cellular. "In certain areas, apparently where the process is most intense, there are abundant accumulations of polymorphonuclear leucocytes. Here the disintegration of the tissues is most evident, and the leucocytes themselves are frequently fragmented and in an advanced stage of degeneration." MacCallum, however, regards these polymorphonuclear leucocytes as reacting to the typhoid infection and not as brought out chemiotactically by tissue necrosis.

Besides these foci of polymorphonuclear leucocytes, the meninges contained great numbers of mononuclear cells, among which are mentioned cells resembling lymphocytes, plasma cells, and all transitions from lymphocyte-like cells to certain very large irregular mononuclear phagocytes having a large vesicular nucleus and abundant ground-glass-like pink protoplasm.

The arteries showed lifting of endothelium by exudate in a form of arteritis not specific for typhoid meningitis but also shown in pneumococcus and streptococcus meningitis.[11, 12, 13] Hektoen's earlier work on tuberculous meningitis may be reviewed in this connection.[14]

It is the relative abundance of the large phagocytic cells which distinguishes typhoid meningitis from other forms. But, although attention has been focused upon the high content of mononuclear phagocytic cells in typhoid meningitis, the occurrence of these cells does not appear to us so remarkable as that of numerous polynuclear leucocytes evoked by Bacillus typhosus.

MacCallum's finding of polynuclear leucocytes in the meninges corresponds well with ours, but the cells in MacCallum's case occurred more in certain foci where disintegration of fixed tissues was most evident.

It seems, then, that the data of Ohlmacher's and MacCallum's cases as well as of our own point to the possibility that the typhoid bacillus, under certain circumstances and notably in the meninges, may act as a pyogenic organism. A case of purulent typhoid meningitis, recently reported by Henry and Rosenberger,[15] appears to resemble ours in the cell-contents of the meninges. This case is described as showing a large number of polynuclear and mononuclear cells, but the large phagocytic cells did not predominate.

With respect to this point it may be noted that MacCallum's case showed the course of a typhoid fever over three weeks long until death, complicated by cerebral symptoms at least two weeks in duration. Henry and Rosenberger's case lasted nine days. Our case had acute symptoms, probably due to bronchopneumonia, for a week, and unconsciousness lasted but two days. Moreover, whereas MacCallum's case, in common with most of those reported, possessed the usual lesions of typhoid fever, the other two cases are less easily to be pressed into the class of typhoid fever. The case of Henry and Rosenberger showed lesions possibly consistent with early typhoid fever (acute catarrhal enteritis with enlargement of Peyer's patches and mesenteric lymph nodes), but scarcely consistent with extensive toxic effects elsewhere. Our own case showed one feature in common with typhoid fever, enlargement of mesenteric lymph nodes, but there is little evidence that typhoid toxine has produced extensive effects in this case. It would seem simplest, therefore, to take the phagocyte-content as indicating roughly the duration of the disease and the degree of endeavor to rid the meninges of necrotic material. There seems to be very little evidence from any of these cases that the typhoid bacillus has produced in the meninges a special accumulation of phagocytic cells.

It will be remembered that Mallory's hypothesis concerning the specific proliferation of endothelial cells in typhoid fever maintains that this proliferation is due to the toxine of the bacillus and not to the direct action of the bacillus itself. Mallory could not demonstrate any relation between the situation of the organisms and the character of the lesions.

In typhoid meningitis we may be dealing not with the effects of typhoid toxine alone, but also with the direct effects of the bacilli themselves. Polynuclear leucocytosis in the meninges appears to be a more characteristic feature than the accumulation of large phagocytic cells.

VII. EXPERIMENTAL TYPHOID MENINGITIS IN THE GUINEA-PIG. — The hypothesis is raised, by a consideration of the data of Ohlmacher's, MacCallum's, Henry and Rosenberger's, and our own cases, that the typhoid bacillus may in the meninges produce an exudation of polynuclear leucocytes. This effect of the bacillus, if demonstrable, would be of a different order from the proliferative stimulus of the typhoid toxine, though the effects of both bacillus and toxine may be together visible in any one region, as a combination of large phagocytic elements and polynuclear leucocytes.

Since the issue in a fatal human case is clouded by possible preëxistent phagocytes and by the well-known tendency of the meningeal tissues to exhibit large phagocytic cells in every kind of tissue necrosis, it seemed desirable to see what the typhoid bacillus might do in a clear field.

The best results in this direction appear to have been obtained by Tictine[16] of Odessa, using rabbits, guinea-pigs, and susliks. Tictine trephined and made subdural inoculations. Abscesses at the site of inoculation were produced in rabbits.

Bacillus typhosus was recovered in the brain as late as twelve days after inoculation. Inflammatory edema occurred within twenty-four hours and suppuration within three days. The experimental meningitis of the suslik took a slower course than in the rabbit and showed marked individual variations. Bacillus typhosus was recovered from suslik brain as late as thirteen days after inoculation. The guinea-pigs used succumbed in twenty-four hours. Blood infections, as indicated by positive cultures in the spleen, were not infrequent in Tictine's animals.

In order to parallel results with work on other organisms[17, 12, 13] we preferred to use the guinea-pig. To avoid the direct effects of cerebral trauma we employed the method of orbital injection after cocainization, already employed in work with other organisms.[12, 13]

We have been able to recover Bacillus typhosus in small numbers from the base of the guinea-pig brain as late as ten days after orbital inoculation. The brain of a guinea-pig similarly inoculated and killed after fourteen days proved to be sterile.

Numerous colonies of B. typhosus were cultivated from the base of the brain five days after inoculation. Thereafter, if our series represents general conditions, the bacilli quickly diminish in number in the guinea-pig.

The same culture (derived from the present case) injected in small quantity into the peritoneum kills overnight, producing a profuse exudation containing polynuclear leucocytes. Such a guinea-pig contains B. typhosus in the heart's blood, but the brain is apt to be sterile.

On the other hand, with our orbital inoculations, we have in no case produced a septicemia with B. typhosus. Probably, therefore, our histological findings in the nervous system are not to be taken as phenomena of a general infection.

The histological study of tissues from a series of guinea-pigs inoculated by way of the orbit with B. typhosus shows that the lesions produced are mild though quite definite. In general it may be said that the critical phase of the disease produced comes later than with the pyogens studied in previous papers. The base of the brain from the fifth to the seventh day shows the most acute lesions, consisting in a diapedesis of blood globules and an exudation of polynuclear leucocytes, together with serum.

Inoculations with Micrococcus aureus, previously reported, showed the acute inflammation at its height in three days. The pneumococcus inoculations gave more variable and less acute lesions, in the sense that mononuclear elements are admixed with polynuclear leucocytes comparatively early, and the height of the polynuclear exudation comes about the fourth day. The streptococcus inoculations correspond in main features with the pneumococcus inoculations.

In the typhosus inoculations, mononuclear elements arrive in the vessels and in the pial meshes by the seventh day.

On the tenth day the exudate has diminished in quantity, the cells and albuminous materials are found fused together in a seminecrotic mass including pyknotic polynuclear cells, and the vessels no longer give evidence of the arrival of fresh exudative cells.

By the fourteenth day the disease is virtually past, and traces only of old exudate are found. Sections from various parts of the nervous system stained for fat (Marchi) demonstrate few or no fatty changes until the seventh day, but are thereafter demonstrable in considerable quantity throughout the decline of the exudative disease. At fourteen days there are still many fibers showing black markings, and at this time numerous cells phagocytic for fat have made their appearance. The most extensive blackenings occur in cranial nerves. Thus it is interesting that the locus of severe fatty change is identical with that of most voluminous cellular exudation, but the time-relations of the two processes differ, the fatty change running behind the exudation by some days.

Parallel inoculations have been made with B. coli and paratyphosus *a* and *β*. These will be reported in a comparative review at a later date.

VIII. Conclusions.

The points of the present paper are as follows:

1. A classical case of taboparesis, with previous history of syphilis, but without history of typhoid fever, succumbs after a week's acute illness to bronchopneumonia and to purulent cerebrospinal meningitis.

2. A typical strain of Bacillus typhosus was isolated in pure culture from a swollen mesenteric lymph node and from the meningeal pus. The blood failed to yield Bacillus typhosus. There were no typhoidal lesions in the intestines.

3. The meningeal exudation contained polynuclear leucocytes in great numbers. This finding, in connection with the older findings of Ohlmacher, W. G. MacCallum, and Henry and Rosenberger, leads to the hypothesis that Bacillus typhosus within the meninges may exert a directly pyogenic action. Should this hypothesis be upheld, the direct action of the bacillus stands in sharp contrast to the proliferative effects of the typhoid toxine described by Mallory in the intestine, lymph nodes and elsewhere in the viscera. The indications are, therefore, that Bacillus typhosus may have two separate effects, the one produced by a diffusible toxine (Mallory) characteristically in the intestinal tract and the other produced in the meninges either by direct local action of the bacilli or through an endotoxine, due to destruction of the bacilli.

4. In confirmation of the results of Tictine, Bacillus typhosus was experimentally found to inflame the meninges of guinea-pigs. In accordance with the hypothesis stated above, guinea-pig brains proved to show an exudation containing many polynuclear leucocytes. Mononuclear elements arrive by the seventh day after inoculation.

5. Research is desirable to determine whether the local action of Bacillus typhosus in the meninges is, or is not, of endotoxic type.

REFERENCES.

1. Rufus Cole. Typhoid meningitis. Johns Hopkins Hospital Reports, xii, 1904, 379–410.

2. Wentworth. A case of meningitis due to the typhoid bacillus. Archives of Pediatrics, xvi, 1899, 824–833.

3. Mallory. A histological study of typhoid fever. Journal of Experimental Medicine, iii, 1898, 611–638.

4. Mallory. Loc. cit., 632–633.

5. Mallory. Loc. cit., 622–625. Also, Necroses of the liver. Journal of Medical Research, vi, 1901, 264–280.

6. Mallory. Journal of Experimental Medicine, loc. cit., 626–7.

7. Mallory. Journal of Experimental Medicine, loc. cit., 636.

8. Ibid. 631–633.

9. MacCallum, W. G. Meningitis due to Bacillus typhosus. Johns Hopkins Hospital Reports, xii, 1904, 411–419.

10. Ohlmacher. Clinical and pathological features of two cases of typhoid meningitis. Journal of American Medical Association, 1897, 419–423.

11. Councilman. Acute meningitis. Journal of American Medical Association, 1905, 1002.

12. Southard and Keene. A study of brain infections with the pneumococcus. Journal of American Medical Association, Jan. 6, 1906.

13. Southard and Stratton. A study of acute leptomeningitis (Streptococcus pyogenes). Journal of American Medical Association, Oct. 20, 1906.

14. Hektoen. The vascular changes of tuberculous meningitis, especially the tuberculous endarteritis. Journal of Experimental Medicine, i, 1896, 113–163.

15. Henry and Rosenberger. Purulent cerebrospinal meningitis caused by the typhoid bacillus, without the usual intestinal lesions of typhoid fever. American Journal of Medical Sciences, February, 1908, 240–244.

16. Tictine. Contribution à l'étude de méningites et des abcès produits par le bacille de la fièvre typhoide. Archiv. de Med. expér., vi, 1894, 29.

17. Southard and Keene. A study of acute hemorrhagic encephalitis (Staphylococcus pyogenes aureus). American Journal of Medical Sciences, March, 1905.

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Dementia Præcox, Paranoid, Associated with Bronchiectatic Lung Disease and Terminated by Brain Abscesses (Micrococcus Catarrhalis)

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DEMENTIA PRÆCOX, PARANOID, ASSOCIATED WITH BRONCHIECTATIC LUNG DISEASE AND TERMINATED BY BRAIN ABSCESSES (MICROCOCCUS CATARRHALIS).*

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(*From the Laboratory of the Danvers Insane Hospital.*)

WE present here the analysis of a case of delusional insanity. During life the case was thought to belong possibly in Kræpelin's group of dementia præcox. One main interest of the case lay in the fact that, by a little emphasis of certain features, the delusions could be regarded as of psychogenic origin, as a malignant elaboration of ideas following a personal disfigurement. There were, however, certain other features rendering a purely psychic origin doubtful for these delusions. Notable among these other features are the autopsy findings, which point to a somatic disease coincident in time with the mental disease, an obstinate lung disease with frequent periods of toxemia. Whatever conclusions are warranted from these features, the case is in itself interesting and, particularly in respect to the chronic meningitis and brain abscesses found at autopsy, presents some data requiring special consideration.

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* Read at a meeting of the Boston Society of Psychiatry and Neurology, February, 1908.

I.

The subject of this history showed few peculiar or striking traits until the age of twenty-five, when, upon the Fourth of July, 1902, his face was disfigured by powder from a small cannon. Thereafter his mental attitude was altered and eventually developed into a picture characteristic of dementia præcox, but with delusions of negation. Meantime a chronic pulmonary disease, with multiple abscesses, was developing and giving rise to the suspicion of phthisis. In 1907 the patient died, was autopsied at the Danvers Insane Hospital, and showed chronic abscesses in many organs.

Of special interest was the discovery of multiple abscesses in the brain. The cell-contents of the meninges were such that a chronic meningitis, possibly dementia paralytica, might have been suspected.

A brother, two years older than patient, is living, in good health, without peculiarities. Patient's father, a nurse, still living, has no peculiarities. Patient's mother died in patient's early life in childbirth, having had poor health, fainting spells and dropsy during pregnancy. A maternal uncle died of tuberculosis. Both grandmothers are said to have died of paralytic shock, both grandfathers of gangrene of the foot. There is no suspicion of mental disease in the family. The family seems to have been American throughout.

The patient made good recoveries from ordinary children's diseases. Occasional headaches, for which no cause is known, affected the patient from eight to fourteen years of age. The patient attended public schools in New York until sixteen years of age, worked as errand boy and in other capacities until nineteen, and followed chair making (ten to thirteen dollars a week) until about the time of his accident. Pneumonia and pleurisy in early life, according to patient. Gonorrhea at twenty-three. No history of syphilis. The patient averred that he had drunk excessively (three to ten glasses of whiskey almost daily) for a number of years; no delirium tremens, no arrests. He is described as reticent, but usually cheerful. Unmarried.

July 4, 1902, patient was injured by the premature explosion of a cannon, and his face was blown full of powder. He was carried to the Cambridge Hospital (for access to whose records we are obliged to Dr. L. S. Hapgood), where he was operated on for traumatic cataract of the left eye. There is no record of mental change during his three weeks' stay at the Cambridge Hospital.

After leaving the hospital patient became rather depressed and worried over his disfigurement. The depression deepened. Patient became inactive and late in December, 1902, grew much worse, talked little, but said he was losing his reason and would never get well.

Jan. 5, 1903, patient was admitted to the McLean Hospital for the Insane. We are indebted to Dr. G. T. Tuttle for the following abstract of events till his discharge Feb. 20, 1903.

During his stay in the hospital he was at first much depressed, but gradually improved. At first he said he could not go out and meet people " as they all know " of his case, that he was " forsaken by everybody," that he was too weak to dress, that there was no case in the hospital like his. He was mentally quite clear, was perfectly well oriented, but seemed a little worried. He gave in detail the story of his illness, adding to the above that about two weeks before entrance he experienced a peculiar " lifting " sensation, and since then his feelings are different, his senses are gone, he has no affection for anybody. He thought that his masturbation was the cause of it all, and this was his principal worry.

During the first of his stay he was quite moody and depressed, but after the first of February he began to feel better in spirits, could think more clearly and began to take more interest in things about him. He improved from that time and for the last ten days of his stay he acted perfectly naturally, said that he wished to go home and that he felt able to go to work. At the solicitation of his brother he was allowed to go on a visit on Feb. 20.

Five days after discharge from McLean, patient tried to commit suicide by shooting in the head. He was committed to the Danvers Insane Hospital, March 17, 1903, where he stayed the remaining four years of his life.

The patient at Danvers was of extreme interest for two reasons, (1) on account of the nature and course of a lung disease (variously regarded as abscess and as phthisis), and (2) on account of the mental symptoms which reminded one of certain features in involutional cases.

The course of the somatic disease may be first considered. Upon admission the sequelæ of the Fourth of July accident were obvious in thickly studded powder-marks of face and ears and in corneal opacities of the left eye. Five punctured wounds, the result of patient's suicidal attempt, and a surgical incision above these wounds, were practically healed.

The lung showed dulness over right lower back and there was diminished expansion in this area. The patient was practically normal in other respects save that vision in the left eye was much impaired, the left knee-jerk was diminished, and the biceps, triceps and wrist reflexes could not be obtained. In certain lights the left pupil was larger than the right. There was not, at this time or later, any suspicion of exudative or degenerative brain disease. Although difficult to disengage from frank delusions, the patient's statement that he had been feeling poorly for months may reflect somatic conditions.

Possibly the symptomatic onset of lung disease may be put back in the latter part of 1902. At all events, the physical conditions noted in the chest on admission were quickly translated into symptoms. There was constant coughing. In less than a month after admission patient became extremely weak and coughed up first blood-stained, later muco-purulent, material. The dulness over right lower back found on admission persisted, and, indeed, lasted till death; but the upper part of the chest became dull also. Breathing was suppressed in the right lower back and harsh above.

Two weeks later the cough had subsided and the patient was up and about. The left back now showed diminished fremitus and breathing.

Ten weeks later (about fourteen weeks after admission) blood was again coughed up and the lung disease seemed localized in the right upper lobe. Occasionally the temperature rose to 104° without chill.

Such attacks were more or less frequent features during 1903–1907. Some of the examiners thought the case one of tuberculosis; others, lung abscess. Repeated examinations of the sputum for tubercle bacilli failed to show any, except a few upon one occasion in

1903. In view of the post-mortem examination, it seems best to regard this finding as accidental.

In December, 1906, patient had severe hemorrhages and brought up thick mucous. Although no tubercle bacilli could be found, the patient was placed in the building for tuberculous patients and ran a constant temperature of variable height. A week before death patient developed abscesses of left arm and of right great toe, containing foul, thick, dirty-brown pus.

In view of the clinical course of the case and the post-mortem findings described below, it seems that the chief features on the somatic side may be explained by fresh outbreaks of lung disease with invasion of greater and greater areas, finally involving the whole lung with abscesses and pneumonic reactions of various ages. The patient was toxemic at various times and may even have been septicemic at times, as at the close of life.

Turning to the psychiatrical side, we find a constant picture of depression, personal delusions of a self-accusatory and negating cast, with a tendency to delusions involving the rest of the world. Certain delusions about his viscera are not inconsistent with the somatic disease in progress. The mental picture varied in severity, and the symptoms came in the form of attacks, sometimes with katatonic excitement. The katatonic features of the case became more characteristic toward the last. During the toxemic periods due to the lung disease patient was quiet, but on questioning revealed depressive delusions having relation to his somatic condition.

The following notes from the clinical records (for which we are indebted to Drs. H. W. Mitchell and C. B. Sullivan) show these points more in detail.

Examination of March 18, 1903: Patient in all respects normal except for depressed emotional expression, which, however, was only appropriate to the delusive ideas centering upon himself and his unhappy condition. He said he had been feeling poorly for months and in December vowed he would give up drinking, but on New Year's day drank once more. "On New Year's day I had an awful time. Could not do anything. Came to the North Union Station and a flash came over my head. My brain was paralyzed. All my troubles left me and I have been no good since. My spirit was taken away and I don't know how I am to die. I have got no future. I feel awfully. Haven't been like other people since then. I can't work — got no power unless some one tells me. Couldn't even get bullets into my head because skull was thick and brain was small. I am the worst thing that ever lived, worse than a murderer. Given up by God — the lowest thing that can be." "I never was just right, but I didn't know enough to have any trouble. I thought I knew everything until I lost my spirit. I have always been a d—d fool. Worse than that; worse than anything could be." Irritability on leading questions about mental disease. Abject depression and weeping when speaking about himself.

Conversation March 25, 1903. "You never saw anybody like me. You can't understand my case. I was born different than any one else. I got no spirit of God. It's awful. I have got a good father and good folks, but there is no hereafter for me."

April 7, 1903 (about a week before a severe pulmonary attack), patient complained that his viscera had become changed, that he had coughed out his lungs, that his spirit had gone.

April 13, 1903. "I am dead, that is all there is about it. The dead can talk and move around in the world. Does it not say so in the Bible? Does it not say a dead man shall walk erect? I can stand every test for a dead man."

For months, and throughout 1904, patient was depressed, slow in movements, a little seclusive and failed to express spontaneously any delusions. He would sometimes agree that former ideas were delusions. He was sometimes comparatively cheerful.

Early in 1905 depression deepened, apprehensiveness, suicidal and "peculiar" ideas developed. Feb. 13, 1905, patient had a fainting spell, but got into bed before it came on, thought he was dying, and his heart seemed to stop. "Brain all gone, ran out through spinal cord, skin rotten, no sensation." On conversation agreed that his brain was not yet wholly run out, and appreciated that his ideas were morbid.

Feb. 15, 1905. "I haven't got good news for you to-night. The world is coming to an end. The devil has been pounding on the walls all day. It must have been the devil. Who else could it have been? I would like to go away and leave this world. The world is going to be burned up, it is so wicked, and he is the cause of it all." Patient also said about his somatic disease, "This is leprosy I am spitting up." When physician suggested that he prepare for death, he was quite willing for the event to occur at once. Patient thought McKinley's death was in some way due to him, having been so informed by God. Feb. 19, tried to commit suicide by choking. Thereafter grew retarded and disinclined to keep oriented for time and to think. Such depressive ideas as the following were prominent: that he was the cause of the end of the world, that the world is degenerating, that he is to be cut up and put down the hopper, that he is nothing more than manure.

March 8, 1905. Agitation, worry, slow anxious wandering about ward, weeping. " Seems as if everything I do is wrong, but I don't think it is." *Q.* " What is wrong ? " *A.* " Well, last night I didn't want to go to bed, and they had to take hold of me. There is Christ there in that last bed (pointing to a general paretic) and he can't help me." Then began to pray, saying: " Have mercy on us and help those who are afflicted and I have wronged, and I wish that I might have the devil taken out of me, and if there is any good in me that I might have life sometime and be washed out that I might have life sometime." Asked to whom he was praying says, " I don't know whether it is God or the devil. God is mighty over all."

April 13, 1905. Sitting in chair, apparently quiet, but on seeing physician, patient became agitated, said, " The world came to an end, and I am wild," began to grind teeth and snarl, tried to bite physician's hand lain on patient's shoulder, clenched fist, assumed an attitude as if about to spring, and, turning his head from side to side, said, " I can't stop this, I can't help it." Similar " wild beast " simulations came at intervals during two months. Occasional suicidal attempts by strangling.

Nov. 7, 1905. Kept left eye closed and left side of mouth drawn up, explaining mannerism by saying that he took medicine that entered eye. Orientation and memory perfect. Said he had passed both ends of the world and got behind everybody. "When I spit, it goes right back into my body again." "Somebody is bringing all the heavens down." "I am murdering the whole world and can't help it."

Occasional excited spells, with running up and down the halls and a variety of bodily contortions. The most common movement was a turning of body from left to right with a sudden jerking of head backward and a flow of irrelevant disjointed talk.

Throughout his bedridden condition in 1906–7 patient maintained orientation, memory and social relations very well and was little disturbed.

Thus, during his Danvers life, the delusions varied more in their spontaneous expression than in their qualitative content and were gradually growing severer and more comprehensive in the topics involved. Katatonic excitement was a feature in 1905, and a few mannerisms developed later. Peculiar contortions came in 1906. After December, 1906, the somatic disease got the better of the motor expression of patient's delusions. Further analysis may be deferred till the autopsy findings have been reviewed.

II.

The autopsy, forty hours post mortem, was performed by the writers. The anatomical diagnoses are as follows, arranged in groups so far as possible with dates of origin.

CHRONIC.

Bronchiectases of lungs, with *abscesses.*
Fibrosis of posterior half of right lung.
Bilateral chronic obliterative pleuritis.
Chronic fibrous auricular endocarditis.

Chronic fibrous pericarditis (milk patch of right ventricle).

Chronic gastritis.

Slight *aortic sclerosis.*

July, 1902.

Gunpowder granules in face and ears.

Corneal opacities of left eye and (slight) right eye.

March, 1903.

Scars of bullet wounds of right temple.

Bullet in right temporo-parietal suture.

Perforation of skull at pterion, with focally *adherent dura mater* and slight *localized leptomeningitis.*

Small old *lacerations of cerebrum* beneath intact inner table under imbedded bullet.

RECENT.

Abscesses of lungs.

Organizing pneumonic foci.

Acute pneumonia.

Swelling of bronchial lymph nodes.

Abscess of left forearm (surgical incisions).

Onychia of left hallux (surgical removal of nail).

Abscess of left chest.

Abscesses of kidneys.

Abscess of spleen, with local *acute peritonitis.*

Multiple abscesses of brain, involving

1. *Left second and third temporal gyri.*
2. Tip of *left occipital lobe.*
3. Tip of *right occipital lobe.*
4. Posterior half of *left cerebellar hemisphere.*

The details of the protocol follow: White male, 163 cm. long. Development good. Nutrition fair. Rigor mortis, general and moderate except in left elbow. Subcutaneous tissues of the upper third of the left forearm are infiltrated with pus, having a foul odor. Upon incision, pus is found to affect not only the subcutaneous tissues, but also the superficial muscles, but does not involve either the bones of forearm or the joints of the elbow. Two surgical incisions of the left elbow region of recent date. Onychia of one left hallux without involvement of bone. Nail of the left hallux has been removed surgically. The muscles of the left foot are less rigid than those of the right. The subcutaneous tissues of the face and of the anterior aspect of both ears are filled with powder granules. Depression with cicatrix, 3 m. in diameter by 0.5 cm. deep, lies at a point 3 cm. posterior to malar border of orbit and 3 cm. above zygomatic process.

Subcutaneous fat of abdomen 1.5 cm. deep. Subcutaneous fat in tissue overlying right second and third rib with intercostal muscular tissue show infiltration with pus which wells up from a small cavity into the muscular tissue from an abscess cavity in the lung tissue below.

Peritoneal cavity. — The free surface of the spleen shows a thin sheet of grayish fibrin of recent formation overlying an abscess cavity of the spleen tissue, but extending several centimeters beyond the region of the abscess. Beneath the peritoneum of the lesser cavity overlying the pancreas, at a point about midway of the body, is an abscess 1.5 cm. in diameter involving both subperitoneal tissue and pancreatic tissue.

Omentum moderately filled with fat. Appendix buried with adhesions. Intestinal tract not remarkable. Mesenteric lymph nodes not enlarged.

Pleural cavities. — Both obliterated by dense old adhesions which are firmest in the right back, especially in the middle and lower portion.

Pericardial cavity. — Not remarkable. Finger-nail-sized milk patch over right ventricle opposite the middle point of the intra-ventricular septum. Pulmonary arteries opened in situ show fluid blood and cruor clot.

Heart. — Weight, 245 gm. Muscle firm and red. Inner surfaces of auricles are of a brownish-gray color. Valves not remarkable. Pulmonary arteries normal. Chambers contain chicken fat and cruor clot.

Measurements: Tricuspid valve, 8.5; mitral valve, 7.0; aortic valve, 6.5; pulmonary ventricle, 11.5; left ventricle, 1.5; right ventricle, 1.5.

Lungs. — Left, 585 gm. Right, 635 gm. There is no portion of the lungs which fails to show exudate. Posterior and central portions of both lungs contain numerous abscess cavities which show gray, rough, shaggy walls and contain slightly creamy yellow pus. No extensive connection was demonstrated between the abscess cavities and bronchi. The lung tissue outside of the abscess cavities was dark red, moist and friable. The posterior half of the right lung is remarkably tough and is provided with an extensive surplus of fibrous tissue. Bronchi reddened. Pulmonary vessels not remarkable. Bronchial lymph nodes, swollen, but fail to contain foci of tuberculosis.

Spleen. — Weight, 235 gm. In the middle of the diaphragmatic surface of the spleen is a dark colored area of fluctuating consistence bearing a slightly grayish center, from which, with slight manipulation, pus may be made to well forth. On section the abscess is found to measure 2.5 x 1.5 cm. in diameter and to lie nearer the diaphragmatic surface of the spleen than to the hilus. The walls are rough and shaggy; the contents, creamy pus. The spleen substance in general is of grayish-pink color and very pulpy. The Malpighian bodies cannot be made out in the grayish-pink substance. Accessory spleen, 1.2 cm. in diameter, lies in connective tissue opposite the splenic flexure.

Gastro-intestinal tract. — Esophagus not remarkable. Stomach walls are thin and smooth. The rest of the intestinal tract is normal throughout, although explored carefully to discover ulceration.

Liver.— Weight, 1,765 gm. Border slightly rounded. Several so-called post-mortem ischemic areas are found, but no evidence of tuberculosis. Consistence slightly diminished. Color slightly translucent, grayish-pink. Gall bladder not remarkable.

Adrenals. — Show no evidence of focal lesion.

Kidneys. — Weight, 375 gm. Strip with abnormal ease. Substance was of a slightly opaque gray-pink color, generally suggesting the appearance of acute nephritis. Both kidneys show several abscesses, from 0.5 to 3.0 cm. The abscesses resemble those of the pancreas, lungs and brain, and are most numerous and extensive in the right kidney. Pelves, ureters and bladder walls not remarkable.

Testes thread well.

Aorta. — Shows a few punctate spots of yellow color along the border of the sinuses of Valsalva.

Head. — Covered by thick black hair. On the right side, two finger-breadths posterior to the orbit and on a level with it, is a depression in the bone into which the ball of the thumb fits, having a firm base. A little posterior to this, just above the ear, a sharp prominent mass is felt just under the skin, about the size of a pea. On stripping back the scalp, which is of normal thickness throughout, this mass is found to be a flattened bullet, approximately .22 caliber, firmly lodged in the skull cap, its entrance point lying in the temporoparietal suture line just above the ear. The depressed area felt on external examination is found to be a perforation in the bone in the neighborhood of pterion, 1.8 cm. in size, the base formed of tough fibrous tissue which when raised exposes the brain to view. Except for a slight blackening of the tissue immediately surrounding these two regions, the scalp is of normal appearance. *Calvarium*, except as noted above, is normal; on removal it is seen that the bullet does not penetrate the inner table. *Dura* is adherent to edges of perforation; elsewhere not abnormal except that it appears everywhere so thin that the convolutions of the brain are easily visible through it. *Pia* generally normal. There is, however, very slight injection over the fossa Sylvii directly under the perforation in the skull, and a few adhesions to the dura at this point. In the process of extracting the brain a large abscess in the left lobe of the cerebellum is exposed. This abscess occupies nearly one half of the lobe in its posterior portion and contains thick, creamy, foul-smelling, puriform material. On further examination, several more similar areas are found as follows: (1) An abscess the size of an English walnut occupying parts of the second and third temporal gyri in the left. Smear from this was similar to that from the cerebellum. (2) A small softened area occupying the tip of the occipital lobe in the region of the gyrus lingualis. On section pus exudes apparently from just under the cortical gray. (3) A similar area on the other side in almost homologous position. (4) A diffusely softened area over one parietal region.

Convolutions are of normal size and in unaltered regions the cortex appears of normal depth. Fluid from the third ventricle is not purulent.[1] On the surface of the convolutions, directly below the point at which the bullet was found, appear three small brownish areas, slightly depressed, none of them more than 5 mm. in diameter; the center of each is dark brown, the color shading off toward the periphery. On the upper and posterior portion of the right mid-frontal gyrus there is a small dull white patch, 2 mm. in diameter, possibly a little firmer than the surrounding tissue, which has a slight brownish discoloration. No similar masses seen at base of brain. Except for the localized softenings described, the brain is of normal firmness, standing up well from the table. *Vessels* at base normal.

Pituitary gland. — A small, firm, white mass appears about 2 mm. in diameter. *Base of skull* normal. *Middle ears* show no signs of acute or chronic inflammation. The larger *sinuses* opened in situ contain fluid blood and post-mortem clots.

III.

A smear from the cerebellar abscess showed polynuclear leucocytes together with many organisms, some of which stained by Gram and some were Gram-negative. No tubercle bacilli could be demonstrated. Two guinea-pigs inoculated subcutaneously with pus from cerebellar and temporal abscesses respectively failed to develop tuberculosis.

Agar plate cultures were made from heart's blood and temporal brain abscess. The heart's blood culture developed one small colony, followed by two more after several days, of a Gram-positive bacillus occurring in chains. This organism was not further studied.

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[1] Cerebrospinal fluid from ventricle shows 795 cells to 100 fields. Lymphocytes, 25%; endothelial cells, 70%; plasma cells, 3%; polymorphonuclear cells, 2%.

Two plates from the temporal lobe abscess developed, one several, and the other numerous, small white colonies of a Gram-negative diplococcus.

This diplococcus grew feebly and, after seventy-two hours, practically not at all. It grew slightly on gelatine without liquefaction. Milk was unaltered by this organism. There was a slight gas production on glucose agar. There was slight stringy growth at the bottom of the bouillon tube in twenty-four hours. On blood agar the organism grew in larger opalescent moist colonies.

These organisms were not quite pure since one colony in the first plate and two in the second turned yellow and proved to consist of staphylococci. These organisms failed to liquefy gelatine.

The Gram-negative diplococcus was thought to be of more importance on account of the appearances in smear. Orbital inoculations were made in two guinea-pigs with the organism growth in bouillon, but the meninges gave no sign of lesion.

It seems probable that this organism belongs in a group related with the meningococcus, with which it corresponds in most particulars. But the peculiar abscess-production in several organs, which we are inclined to attribute to it, may serve to throw doubt on its meningococcal character. It is possible that the organism is a secondary invader in lesions produced in some other way.

We are inclined, however, to identify this organism with the *micrococcus catarrhalis*.

The *micrococcus catarrhalis* was cultivated, first probably by Kirchner,[2] in 1890, but cultivated and first named by R. Pfeiffer (oral communication to Frosch and Kolle[3]). Pfeiffer regards the organism as nearly related to the staphylocci, but as distinguishable therefrom as Gram-negative and as non-liquefying with gelatine.

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[2] Kirchner: Bacteriologische Untersuchungen über Influenza. Zeitschr. für Hyg., 1890, Bd. 9, S . 528.

In practise the *micrococcus catarrhalis* has proved to be harder to distinguish from the meningococcus and the gonococcus, sharing with them the Gram-negative staining and the frequent intracellular occurrence, as well as numerous other characters. Ghon and H. Pfeiffer, 1902, working in Weichselbaum's laboratory,[4] insist that, though the three organisms form a separate group among micrococci, they nevertheless belong to three separate species. The *M. catarrhalis* is the least pathogenic in man, and, under saprophytic conditions, grows more profusely and exhibits more vitality than the meningococcus or the gonococcus.

As a matter of diagnosis, the cultural growth of the gonococcus is distinctive enough. The meningococcus colonies are said by Ghon and Pfeiffer to be a little moister and grayer, more finely granular, as well as always less profuse than catarrhalis colonies. The catarrhalis still grows at temperature less than 20° C. The larger size of individual cocci of the catarrhalis species is said to form anothe· constant feature as against micrococci.

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[3] Frosch und Kolle: Mikrokokkus catarrhalis (Kokkus bei infektiöser Bronchitis). Flügge's Mikro-organismen, 2896, Bd. 2, S. 154.

[4] Ghon und H. Pfeiffer: Der Mikrococcus catarrhalis (R. Pfeiffer) als Krankheitserreger. Zeitschr. für klin. med., 1902, Bd. 44, S. 262.

The localization of the *M. catarrhalis* in man is usually respiratory. The most frequent association is probably that with bronchopneumonia in children. Ghon and Pfeiffer found it 81 times in 132 cases of lung disease. In one case they found this organism alone, in 5 others in highly predominant numbers. Petruschky[5] found the organism in a case of typhoid fever associated with B. typhosus in the spleen, but in pure culture in the liver, kidney, and heart's blood. Weichselbaum[6] reckons this organism as of some importance in bronchopneumonia, but probably as an associated organism.

We have not yet found special statements concerning the association of *M. catarrhalis* with bronchiectatic lung conditions.

IV. HISTOLOGY.

The microscopic examination of the organs of the trunk gave the following results:

Heart not remarkable. Coronary branches thickened.

Lung. — It is difficult to demonstrate satisfactorily the bronchiectatic origin of the abscesses, since the bronchial mucosa has been largely destroyed in the process of abscess-formation. This is especially true in blocks from the central and posterior portion of the lung, where the diagnosis seemed grossly most assured.

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[5] Petruschky: Krankheitserreger und Krankheitsbild. Zeitschr. für Hyg., 1901, Bd. 36, S. 154.

[6] Weichselbaum: Diplococcus pneumoniæ und andere bei entzündlichen Lungenaffektionen gefunden Bakterien. Kolle u. Wassermann, Pathogene Mikro-organismen, 1903, Bd. 3, S. 234.

Recent purulent processes are also found throughout, with extensive masses of bacteria, both cocci and bacilli. The largest masses are coccal.

In places acute pleuritis.

Spleen. — The abscess is walled by leucocytes only, imbedded in a rather coarse fibrin. Extraordinary numbers of delicate bacilli occur within the abscess and have multiplied largely outside the leucocyte bodies. Outside the abscess wall are numerous deeply staining fragments suggesting bacteria, and among these a few characteristic slender bacilli. Polynuclear leucocytes are rare outside the abscess. Numerous plasma cells are found throughout the pulp. The Malpighian bodies are only slightly active.

Liver. — Slight periportal cellular cirrhosis. The fatty change is moderate and largelyremote fromportal spaces.

Pancreas. Slight chronic interstitial process.

Kidney. — The abscesses here are recent and with well-defined reaction of surrounding fixed tissues. In cells and between cells in the interior of the abscess are great numbers of minute organisms in pairs, resembling those of the brain abscesses.

Adrenal. — In the fat tissue around one adrenal there is considerable hemorrhage. Among the blood corpuscles are numerous bacteria. Several large colonies of bacteria with greenish pigment masses included are found in one place.

Cerebral cortex. — The suspicious findings in the cerebrospinal fluid led to an unusually careful search for cortical cell-pictures characteristic of general paresis of the insane.

The result of this search shows that the cerebral cortex of this case is certainly not normal, but that the pictures are far removed from those seen in general paresis.

The cortex is abnormal in several respects. Besides the coarse abscesses mentioned in the gross description, and some smaller ones found on microscopic examination, there is a certain degree of rather active subpial gliosis and a variable reduction in the number of nerve cells in the outer layers. But focal and irregular losses of nerve cells and intracortical perivascular infiltration with mononuclear cells are conspicuous by their absence.

There is a greater degree of subpial gliosis at the sulcal bottoms than over the crowns of gyri. The cells of the layer of small pyramids and to some extent those of the layer of medium-sized pyramids have suffered atrophy in some regions along the walls of the sulci, but except in the right temporal region, in no instance was this condition found above the lips of the sulci.

The cortex of the *right temporal region* will be especially described because we can very probably date its peculiar features precisely, that is, back to February, 1903, when patient shot himself in the head four years and nine months before his death. A cross-section of the right superior temporal gyrus, opposite the point of impact of the bullet, shows a singular atrophy with maintenance of cortical depth. If this atrophy can be related with the old concussion (which seems indicated by the brown spots of limited size beneath the site of the imbedded bullet), it is interesting that the outer layers are scarcely more affected than the inner layers. The maximal cell loss is probably that of the layer of medium-sized pyramids. This layer is in places almost nerve-cell-free, but never quite so, so that a senile atrophic condition is imitated rather than an arteriosclerotic atrophy. Both the layer of small pyramids and the stellate cell layer show a considerable diffuse thinning out of cells. The larger pyramids are somewhat better maintained. There is considerable subpial and medullary gliosis.

DISCUSSION.

We have presented the case of an American youth of average capacity, a chair-maker for some six years, who became insane (depressed, paranoid, suicidal, later at times katatonic) after facial disfigurement in a Fourth of July accident at the age of twenty-five. We were tempted to a more particular study of this case because of the clear-cut features of an autopsy five years after onset (chronic and acute lung disease with abscesses, multiple abscesses of other organs including the brain), which seemed to point to bronchiectases and lung disease of ancient date.

The clinical history and the autopsy findings are so far consistent that a "psychogenic" origin for this case of (possibly) dementia precox can be safely discounted. It seems safe to conclude that the lung disease was already in process of production in the six months subsequent to the episode of facial disfigurement. It is possible that this disease antedated the facial injury and that masses of bacteria in dilated bronchi had begun to affect the patient long before frank pulmonary signs set in.

However this may be, the lung disease, whose progress was carefully followed on account of its clinical resemblance to pulmonary tuberculosis, had a peculiar effect upon the course of the mental symptoms. Both lung disease and mental disease came in attacks, but these attacks did not coincide in time.

The lung disease would affect in each attack a fresh area and was characterized by exhaustion, bloody and purulent expectoration (no tubercle bacilli) and high fever.

During the toxemic phases of the lung disease the patient was quiet, but would yield depressive delusions on questioning. Just as earlier the patient had been depressed ostensibly on account of his disfigurement, so throughout his disease he tended to delusions concerning his somatic condition. (" This is leprosy I am spitting up.") But his delusions were at all times of wider range than his bodily disease (" given up by God," " world is degenerating," "murdering the whole world "), and were sometimes of extreme metaphysical ingenuity (" passed both ends of the world and got behind everybody ").

After some years the paranoid picture had become emphasized by mild and episodic katatonic features (wild beast simulations, mannerisms and peculiar contortions).

It is, of course, possible that the lung disease and the mental disease are merely interpenetrating entities in this case. The autopsy showed that the brain, in common with the kidneys and the spleen and other structures, had undergone abscess-formation. There is, however, no evidence that the brain abscesses were of long standing, and, though the fatal issue was pyemic, it is probable that previous attacks had been merely toxemic, or at most mildly septicemic. The micro-organism engaged in the abscess-formation is not in all respects well-defined, but seems to belong to the *micrococcus catarrhalis* group. There is no convincing evidence that this organism was in any way responsible for the clinical features of the disease as a whole. But it seems not easy to exclude, in a more general way, the presumably highly toxic masses of bacteria and detritus in the pulmonary tissues from the field of factors in the mental disease.

Just as it has long been suspected by some workers that there is a somewhat close relation between lung disease and brain disease (and, in particular, between bronchiectases and brain abscesses), so there may possibly obtain a more delicate and elusive connection between toxic lung conditions and brain conditions. It would be of extreme value could we learn more precisely the paths taken by bacteria and toxins from the lungs to the central nervous axis.

LIST OF THIRTY-SEVEN NEUROPATHOLOGICAL PAPERS, HARVARD UNIVERSITY MEDICAL SCHOOL, 1904-1908.

SERIES OF 1904.

I. Outline of Neuropathology.

E. E. Southard.

II. A Case of Chronic Internal Hydrocephalus in a Youth.

E. E. Southard and W. F. Roberts.

(From Journal of Nervous and Mental Disease, xxxi, 2, February, 1904.)

III. A Case of Cortical Hemorrhages Following Scarlet Fever.

E. E. Southard and F. R. Sims.

(From Journal of American Medical Association, xliii, 12, September, 1904.)

IV. A Case of Glioma in the Sella Turcica.

F. H. Howard and E. E. Southard.

(From American Journal of Medical Science, cxxviii, October, 1904.)

V. A Case of Diffuse Encephalitis Showing the Pneumococcus.

W. N. Bullard and F. R. Sims.

(From Boston Medical and Surgical Journal, cli, 24, December, 1904.)

VI. Anatomical Findings in Two Cases of Korsakoff's Symptom-Complex.

F. R. Sims.

(From Journal of Nervous and Mental Disease, xxxii, 3, March, 1905.)

VII. A Case of Glioma of the Pineal Region.

E. E. Southard.

(From American Journal of Insanity, lxi, 3, 1905.)

VIII. A Study of Acute Hemorrhagic Encephalitis (Staphylococcus Pyogenes Aureus.)

E. E. Southard and C. W. Keene.

(From American Journal of Medical Sciences, cxxix, March, 1905.)

SERIES OF 1905.

I. THE NEUROGLIA FRAMEWORK OF THE CEREBELLUM IN CASES OF MARGINAL SCLEROSIS.

E. E. Southard.

(From Journal of Medical Research, xiii, 5, August, 1905.)

II. A CASE OF CHOLESTERIN STONES IN THE BRAIN AND CORD.

E. E. Southard.

(From Journal of the American Medical Association, xlv, 23, December 2, 1905.)

III. A CASE OF POTT'S DISEASE IN THE MONKEY.

E. E. Southard.

(From Journal of Medical Research, xiv, 2, January, 1906.)

IV. CYSTIC APLASIA OF THE CEREBRAL HEMISPHERES IN AN IDIOT CHILD.

W. N. Bullard and E. E. Southard.

(From Journal of Medical Research, xiv, 2, January, 1906.)

V. DIFFUSE GLIOSIS OF THE CEREBRAL WHITE MATTER IN A CHILD.

W. N. Bullard and E. E. Southard.

(From Journal of Nervous and Mental Disease, xxxiii, 3, January, 1906.)

VI. A STUDY OF BRAIN INFECTIONS WITH THE PNEUMOCOCCUS.

E. E. Southard and C. W. Keene.

(From Journal of the American Medical Association, xlvi, 1, January 6, 1906.)

SERIES OF 1906-1907.

I. OUTLINE OF NEUROPATHOLOGY. 1906.

E. E. Southard.

II. A STUDY OF ACUTE LEPTOMENINGITIS (STREPTOCOCCUS PYOGENES.)

E. E. Southard and R. R. Stratton.

(From Journal of the American Medical Association, xlvii, October 20, 1906.)

III. LESIONS OF THE GRANULE LAYER OF THE HUMAN CEREBELLUM.

E. E. Southard.

(From Journal of Medical Research, xvi, 1, March, 1907.)

IV. On Serum Anaphylaxis in the Guinea-pig.

F. P. Gay and E. E. Southard.

(From Journal of Medical Research, xvi, 2, May 1907.)

V. Diffuse and Focal Lesions in a Case of Late Epilepsy.

E. E. Southard.

(From Transactions of the National Association for the Study of Epilepsy. Sixth Annual Meeting, New Haven, Connecticut, November 8, 1906. Vol. IV.)

VI. Note on Cell-Findings in Soft Brains.

E. E. Southard and M. B. Hodskins.

(From American Journal of Insanity, lxiv, 2, October, 1907.)

VII. Gliotic Cyst of the Right Superior Parietal Lobule.

A. N. Collins and E. E. Southard.

(From American Journal of Insanity, lxiv, 2, October, 1907.)

VIII. The Function of Tonicity in Human Isohemagglutination.

F. P. Gay.

(From Journal of Medical Research, xvii, 3, December, 1907.)

IX. The Determination of the Alexic Activity of Human Blood Serum.

F. P. Gay and J. B. Ayer, Jr.

(From Journal of Medical Research, xvii, 3, December, 1907.)

X. Alexic Activity of the Blood Serum of Cadavers.

F. P. Gay.

(From Journal of Medical Research, xvii, 3, December, 1907.)

SERIES OF 1908.

I. Cyst of Dura Mater Occupying the Left Middle Cranial Fossa Associated with Anomalous Development of the Left Superior Temporal Gyrus.

J. B. Ayer, Jr.

(From American Journal of Insanity, lxiv, 3, January, 1908.)

II. On the Mechanism of Gliosis in Acquired Epilepsy.

E. E. Southard.

(From American Journal of Insanity, lxiv, 4, April, 1908.)

III. A Complicated Case of Brain Tumor.

Charles Ricksher and E. E. Southard.

(From American Journal of Insanity, lxiv, 4, April, 1908.)

IV. MELANCHOLIA WITH DELUSIONS OF NEGATION: THREE CASES WITH AUTOPSY.

H. W. Mitchell and E. E. Southard.

(From Journal of Nervous and Mental Disease, xxxv, 5, May, 1908.)

V. A CASE OF BRAIN ABSCESS SHOWING THE PNEUMOCOCCUS.

R. M. Green.

(From Journal of the American Medical Association, l, May 2, 1908.)

VI.–IX. FURTHER STUDIES IN ANAPHYLAXIS.

I. ON THE MECHANISM OF SERUM ANAPHYLAXIS AND INTOXICATION IN THE GUINEA-PIG.

II. ON RECURRENT ANAPHYLAXIS AND REPEATED INTOXICATION IN GUINEA-PIGS BY MEANS OF HORSE SERUM.

III. THE RELATIVE SPECIFICITY OF ANAPHYLAXIS.

IV. THE LOCALIZATION OF CELL AND TISSUE ANAPHYLAXIS IN THE GUINEA-PIG, WITH OBSERVATIONS ON THE CAUSE OF DEATH IN SERUM INTOXICATION.

F. P. Gay and E. E. Southard.

(From Journal of Medical Research, xviii, 3, xix, 1, June and July, 1908.)

X. A PATHOLOGICAL STUDY OF A CASE OF HYDROCEPHALUS.

Samuel T. Orton.

(From American Journal of Insanity, lxv, 2, October, 1908.)

XI. CLINICAL AND ANATOMICAL ANALYSIS OF TWENTY-THREE CASES OF INSANITY ARISING IN THE SIXTH AND SEVENTH DECADES WITH ESPECIAL RELATION TO THE INCIDENCE OF ARTERIOSCLEROSIS AND SENILE ATROPHY AND TO THE DISTRIBUTION OF CORTICAL PIGMENTS.

E. E. Southard and H. W. Mitchell.

(From American Journal of Insanity, lxv, 2, October, 1908.)

XII. TYPHOID MENINGITIS: CULTIVATION OF BACILLUS TYPHOSUS FROM MENINGES AND MESENTERIC LYMPH NODE IN A CASE OF GENERAL PARESIS, WITH NOTE ON EXPERIMENTAL TYPHOID MENINGITIS IN THE GUINEA-PIG.

E. E. Southard and E. T. F. Richards.

(From Journal of Medical Research, xix, 4, December, 1908.)

XIII. DEMENTIA PRAECOX, PARANOID, ASSOCIATED WITH BRONCHIECTATIC LUNG DISEASE AND TERMINATED BY BRAIN ABSCESSES (MICROCOCCUS CATARRHALIS.)

E. E. Southard and J. B. Ayer, Jr.

(From Boston Medical and Surgical Journal, clix, 27, December, 1908.)

XIV. LIST OF THIRTY-SEVEN NEUROPATHOLOGICAL PAPERS, HARVARD UNIVERSITY MEDICAL SCHOOL, 1904–1908.

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